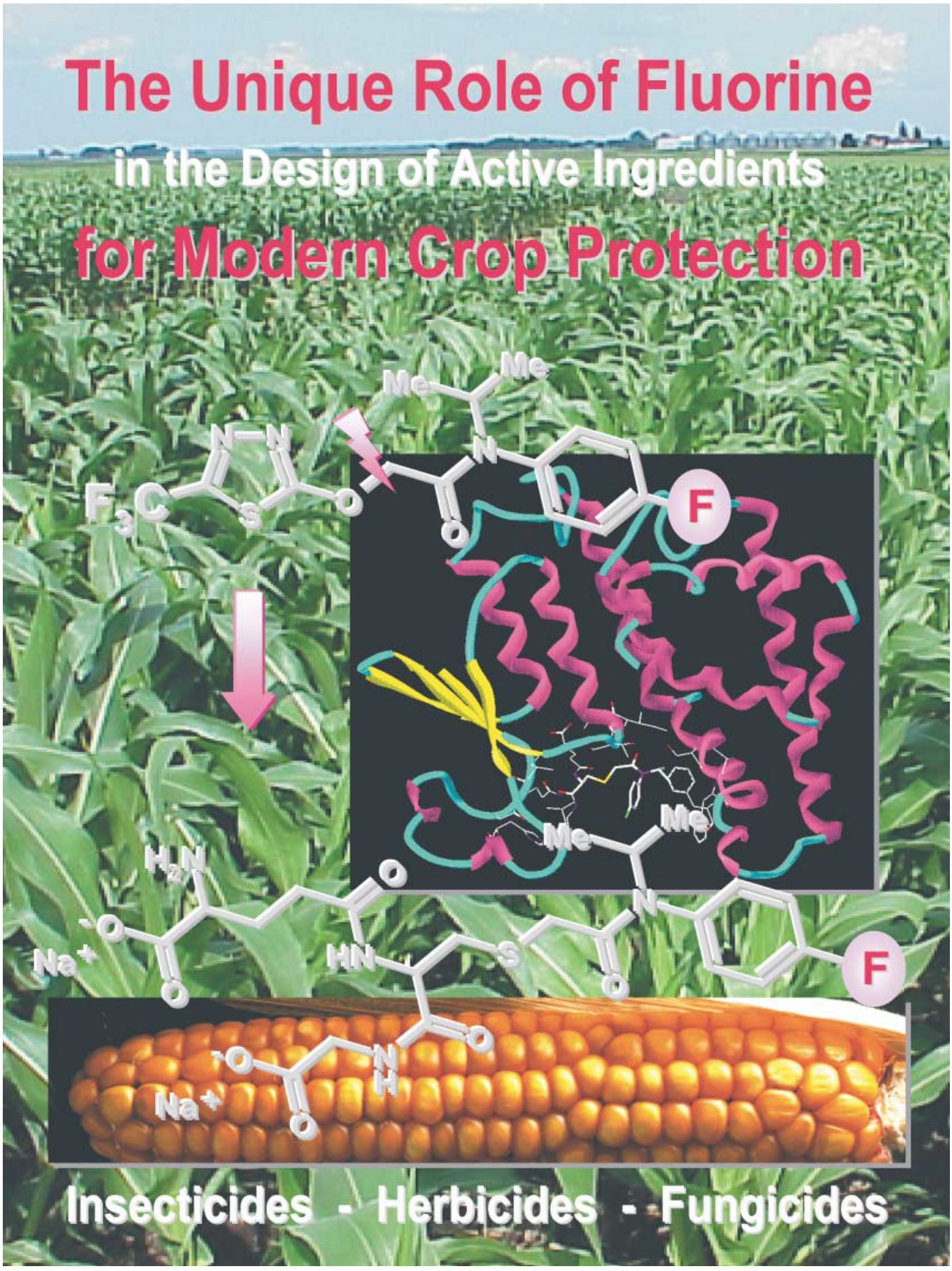

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The Unique Role of Fluorine in the Design of Active Ingredients for Modern Crop Protection

Peter Jeschke*[a]

The task of inventing and developing active ingredients with useful biological activities 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 compounds. However, compounds within a given structural family may exhibit quite different biological activities depending on their interactions with different intracellular proteins like 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 dynamic properties can be improved. In this context, the introduction of fluorine into active ingredients has become an important concept in the quest for a modern crop protection product with optimal efficacy, environmental safety, user friendliness, and economic viability. Fluorinated organic compounds represent an important and growing family of commercial agrochemicals. A number of recently developed agrochemical candidates represent novel classes of chemical compounds with new modes of action; several of these compounds contain new fluorinated substituents. However, the complex structure–activity relationships associated with biologically active molecules mean that the introduction of fluorine 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. Therefore, it is still difficult to predict the sites in a molecule at which fluorine substitution will result in optimal desired effects.

1. Introduction

The number of active ingredients in modern crop protection products that contain fluorine-substituted moieties has increased over the past 30 years. Interestingly, there has been a significant rise in the number of commercial products containing "mixed" halogens, that is, one or more chlorine atom in addition to one or more fluorine atom (Figure 1). Extrapolation of

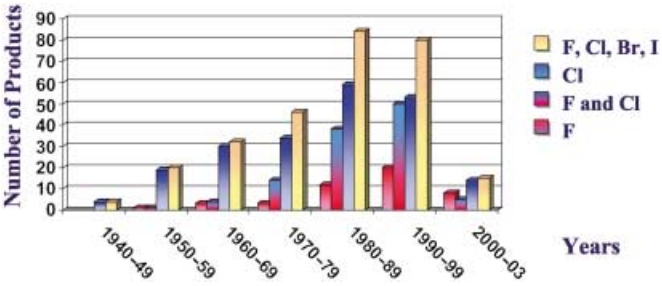

Figure 1. *Launch of halogenated commercial products in the time frame 1940–2003.*

the current trend indicates that a definite growth in fluorine-containing commercial products is to be expected throughout the 21st century. A survey of all halogenated commercial products available in the time frame 1940–2003 shows that fluorinated products (colour coded red in Figure 2) account for more than 28% of the substances on offer. A detailed breakdown of all fluorinated commercial products gives an insight into the current main areas of modern crop protection. According to the present subdivision of the available products, the most common application of fluoro agrochemicals is in herbicides/safeners,[1,2] which represent 54% of products on

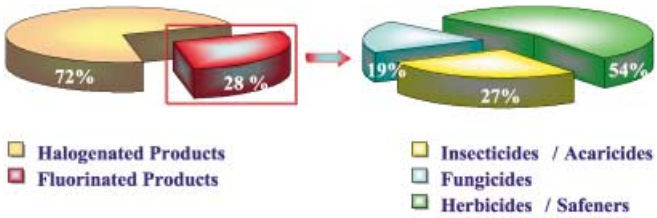

Figure 2. *Breakdown of fluorinated commercial products into insecticides/acaricides, fungicides, and herbicides/safeners.*

the market; 27% are insecticides/acaricides and 19% are fungicides. Surprisingly, the market share of the total crop protection market in 2001 (which accounted for €30 billion) taken by herbicides/safeners was 48%, by insecticides/acaricides 26%, and by fungicides 21%, and these values reflect a similar proportional division of the whole market to that of the fluorine derivatives into these major agrochemical areas. The remaining segment of the market consists of products for so-called nonagrochemical uses like gardening and professional plant care, which in total account for less than 8% of the market. Substituted aryl and hetaryl moieties are of great importance for active ingredients in modern crop protection because two thirds of all known active ingredients for crop protection contain these molecular fragments. The correct selection and

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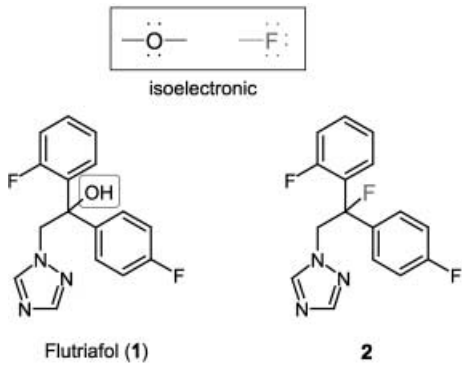
modification of appropriate substituents at the periphery of a molecule and their substitution pattern often play a decisive role in the achievement of excellent biological activity.[3] A critical analysis of all commercial products containing fluorine-substituted aromatic moieties reveals a typical substitution pattern for aryl or hetaryl moieties in insecticides/acaricides, fungicides, and herbicides/safeners, and demonstrates the structural overlap between these products. It is clear that for a long time the most common application of organic fluorochemicals has been in the field of herbicides. In the herbicides commercialized so far, the diversity of aryl and hetaryl moieties and substituents is greater than in other types of agrochemicals such as fungicides or insecticides/safeners. Furthermore, a breakdown of fluorinated commercial products with regard to their level of fluorination shows a statistical pattern: insecticides/acaricides tend to contain at least four fluorine atoms, herbicides/safeners around three fluorine atoms, and fungicides at least two fluorine atoms.

2. The Fluorine Substituent Effect

Why does fluorine play a unique role in the design of active ingredients for modern crop protection? The importance of fluorine in commercial products can be attributed to the well-known physicochemical effects arising from the introduction of fluorine and fluorinated substituents into biologically active molecules.[4] 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.

The steric effect

The small size of the fluorine atom (1.47 Å) is a unique characteristic and its van der Waals radius is similar to that of hydrogen (1.20 Å), therefore, a fluorine atom can mimic a hydrogen atom or hydroxy group (1.40 Å) in a bioactive compound with respect to steric requirements at receptor sites. For example, the fluorine atom was introduced into the broad-spectrum fungicide flutriafol (**1**; Impact, Syngenta)[5] as a chemical isoster of the tertiary hydroxy group, which is essential for the fungicidal activity of the triazole (Scheme 1). The trifluorinated analogue **2**[6] retains some biological activity, even though there is an overall reduction in spectrum.

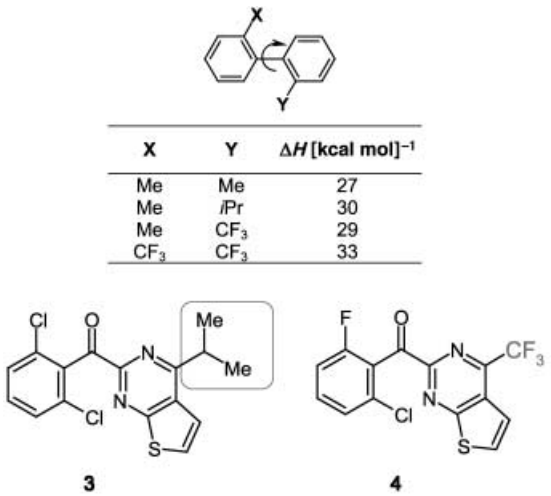


Scheme 1. *The fungicide flutriafol (**1**; Impact, Syngenta) and its trifluorinated analogue **2**.*

In addition, the apparent size of the CF_3 group is comparable to that of the isopropyl group, as demonstrated by measurements of the rotation barriers of appropriate substituted biphenyl systems. The ΔH values calculated by the force field method MMFF94[7] for the isopropyl (30 kcal mol^{-1}) and CF_3 groups (29 kcal mol^{-1}) are approximately the same. The two herbicides **3** and **4** (active against rice and soybean, respectively; Scheme 2) are effective against annual grass weeds and their steric compatibility with target sites is reflected in their different selectivities.[8]

The electronic effect

The high electronegativity of fluorine (4.0, Pauling scale) can have pronounced effects on the electron distribution in a mol-



X	Y	ΔH [kcal mol]$^{-1}$
Me	Me	27
Me	*i*Pr	30
Me	CF_3	29
CF_3	CF_3	33

Scheme 2. *Herbicides active against rice (**3**) and soybean (**4**).*

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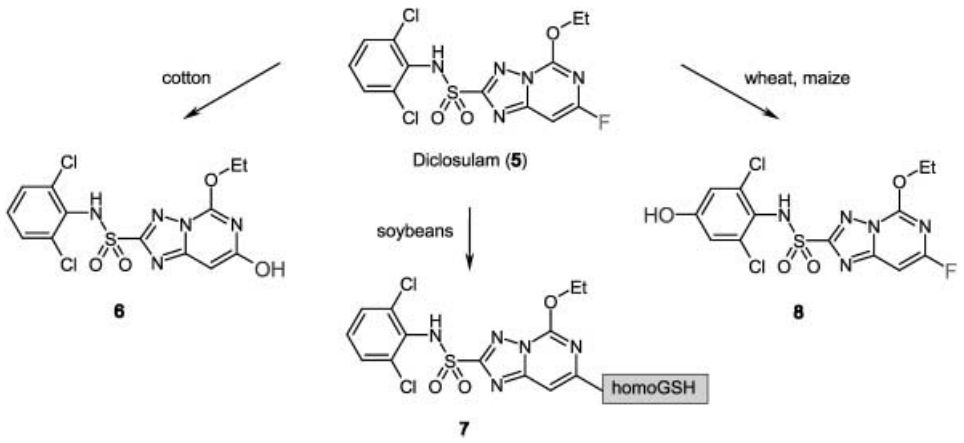
ecule since the presence of a fluorine atom affects the acidity or basicity of neighbouring groups and can create a high dipole moment.[9] Furthermore, fluorine is associated with a fascinating set of electronic effects encompassing both "push" effects, like the $+M$ or $+I\pi$ effects in aromatic systems and the stabilization of α-carbocations ($^{+}CHF_2 > {}^{+}CH_2F > {}^{+}CF_3 > {}^{+}CH_3$), and "pull" effects, such as destabilization of β-carbocations and possibly negative (or anionic) hyperconjugation. Stabilization of tetrahedral transition states and possible hydrogen bond formation or interaction with hydrogen by fluorine have been described as well.



Scheme 3. *Pathways of diclosulam (**5**) metabolism in varoius crop species.*

Stability—metabolic, oxidative, and thermal

In comparison to C–H (98 kcal mol^{-1} at 25 °C), C–N (73 kcal mol^{-1}), and other C–halogen bonds (C–Cl, 81; C–Br, 68; C–I, 57 kcal mol^{-1}), the C–F bond energy of 116 kcal mol^{-1} is large and has significant influence on metabolic, oxidative, and thermal stability. A plot of Hammett σ coefficients against stability for various aromatic ring substituents shows that fluorine and fluorine-containing substituents more strongly influence stability towards oxidation, hydrolysis, and/or soil degradation than the other residues. Electron-withdrawing groups (CCl_3, SO_2NH_2) can stabilize an aromatic ring system to oxidative (or electrophilic) attacks, but too many withdrawing groups may bring susceptibility to nucleophilic attack. Fluorine and fluorine-containing substituents like CF_3 or CF_3O are themselves very stable to attack. Therefore, an increased degradation stability is observed for biologically active molecules or fragments containing substituents from this special group.

The metabolic stability of the C–F bond can be exploited to make a pro-insecticide, for example, 29-fluorostigmasterol.[10] Insects produce cholesterol by dealkylation of phytosterols like stigmasterol through a pathway not found in mammals that involves formation of monofluoroacetic acid and (−)-*erythro*-2-fluorocitrate, which are lethal to insects.

The different metabolic pathways of diclosulam (**5**),[11] a herbicide produced by Dow AgroScience, are guided by the 7-fluorine substituent on the triazolopyrimidine ring system. The predominance of one pathway is very crop specific. In cotton, for example, **5** is metabolized by the displacement of the 7-fluoro substituent on the triazolopyrimidine ring by a hydroxy group (**6**). The soybean selectivity is attributed to facile conjugation with homoglutathione (*homo*GSH), which displaces the 7-fluoro substituent (**7**). In maize and wheat, **5** is detoxified by hydroxylation at the 4-position on the aniline moiety followed by subsequent glycosidation (**8**; Scheme 3).

The effect of lipophilicity

The presence of fluorine substituents in biologically active molecules enhances their lipophilicities, therefore these substituents can influence the in vivo uptake and transport of active ingredients. It seems that this effect is often relevant for fluorinated aryl and hetaryl systems that interact with π electrons (R/π: HO/−0.68, H/0, F/+0.14, F_3C/+0.88, CF_3O/1.04, F_5S/1.22, CF_3S/1.43). Monofluorination and trifluorination of saturated aliphatic groups normally decrease lipophilicity, whereas polyfluorination increases volatility.

Classification in the disjoint principle properties space[12]

The systematic variation of substituents in a molecule has been the subject of various studies in the past. Besides synthetic feasibility and economic considerations, properties such as polarity, size, and H-bonding capacity form the basis for choosing substituents like fluorine and fluorine-containing substituents (F_3C, F_3CSO_2, F_3CO, F_3CS). The disjoint principle properties (DPP), derived from a large set of property desriptors for substituents including fluorine and fluorine-containing groups, can be used to make rational and effective choices. Severeal excellent examples are described below, in the part of Section 5 concerning sulfonylureas; these examples include the successful exchange of the ethylsulfonyl group in rimsulfuron (**92**, R=SO_2–Et) with the trifluoromethyl group to give flazasulfuron (**93**, R=CF_3).

Key physical properties of active ingredients for modern crop protection[13]

Numerous key physical properties of molecules that are important for agricultural uses, like soil behavior, toxicology, systemicity, solubility, volatility, polarity, as well as penetration and so forth, can be influenced or enhanced by fluorine and fluorine-containing substituents. The octanol/water partition coefficient (P) is a guide to soil leaching. A log$P$ value of about 3 is the trigger for potential leaching unless the soil half-life is short. Aquatic organisms bioconcentrate compounds from water

roughly in proportion to the log *P* value. Plant systemicity, for example, xylem mobility,[14] is very limited above a log *P* value of 3.5. Penetration into organisms is strongly affected by the polarity of the active ingredient, for which $\Delta \log P$, the difference between the octanol/water ($\log K_{oct}$) and hexane/water partition coefficients ($\log K_{hexane}$), or the polar surface area provides a good estimate. Both vapour pressure and pK_a values have obvious effects on compound behavior. Most of these key physical properties of molecules for agricultural uses can be influenced or enhanced by fluorine and fluorine-containing substituents. Therefore, the search for fluorine-containing active ingredients and corresponding intermediates by the agrochemical industry carries on.

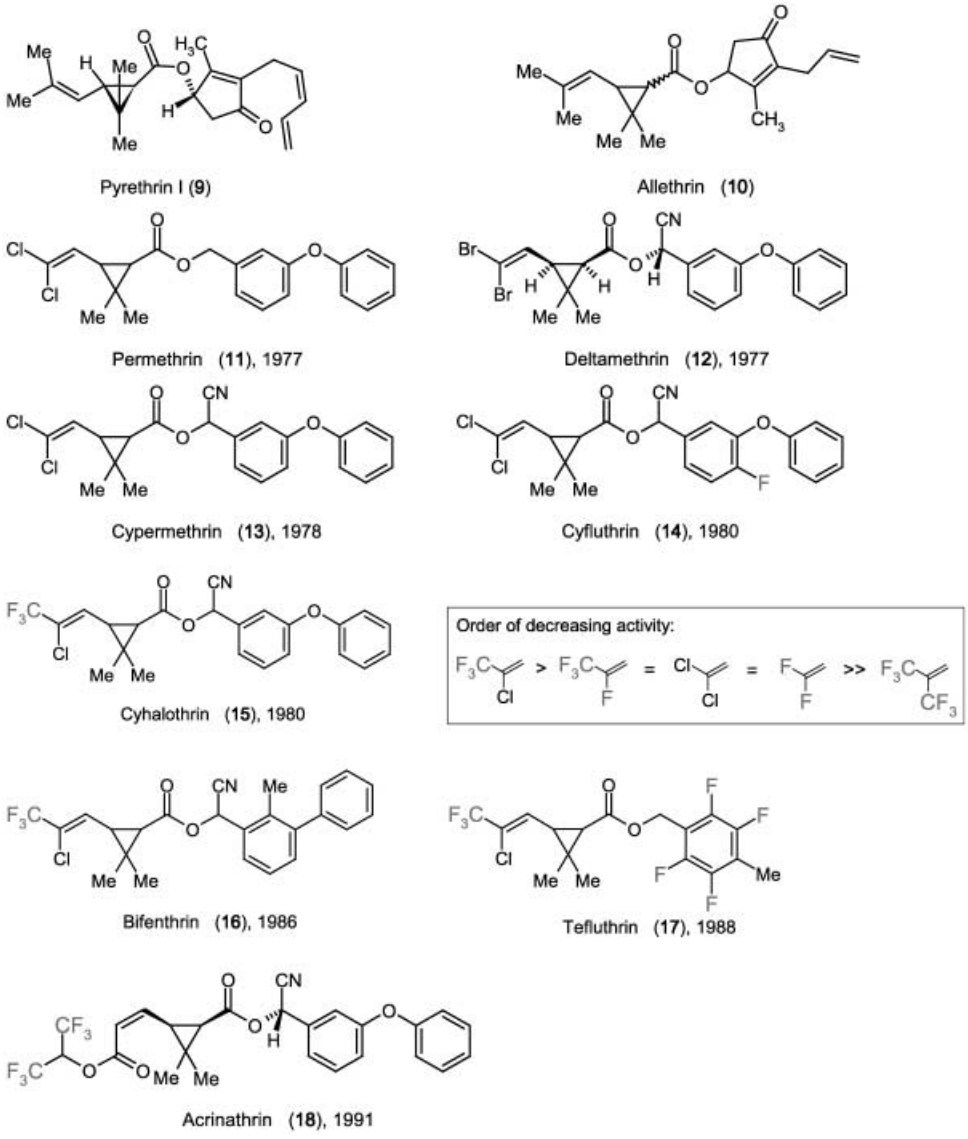
The successful utilization of fluorine and its unique role in the design of active ingredients for modern crop protection can be exemplified by various commercial products from Bayer CropScience in the above-mentioned major agrochemical areas.

3. Insecticides Containing Fluorine

Pyrethroides

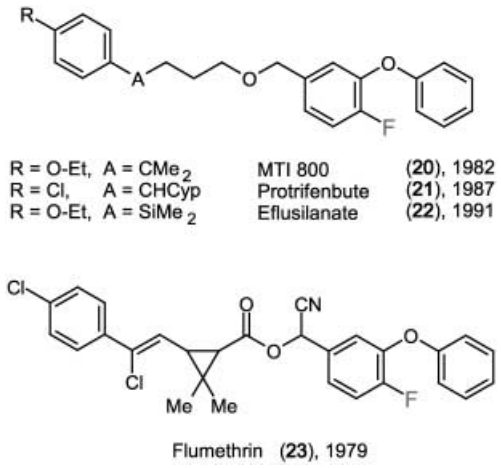
The development of synthetic pyrethroids, which act on the voltage-gated sodium channel, provides a significant historical illustration of the introduction of fluorine into active ingredients.

Shortening and simplification of the pentadienyl side chain of the insecticide pyrethrin I (**9**),[15] which was obtained from *chrysanthemum* flowers, led in the 1950s to the first synthetic and more stable pyrethroid, allethrin (**10**).[16] More than twenty years later, replacement of the cyclopentene alcohol group and introduction of the dichlorovinyl moiety resulted in permethrin (**11**),[17] which is applied to cotton at about 200 g a.i ha^{-}. Insertion of an α-cyano substituent at the phenoxybenzyl alcohol group produced either deltamethrin (**12**), when a dibromovinyl moiety was used,[18] or cypermethrin (**13**) when the dichlorovinyl moiety was retained.[19] Both compounds show significantly enhanced insecticidal activity compared to **9**. Finally, in 1980, the first fluorine-containing pyrethroid, cyfluthrin (**14**),[20] was launched. Cyfluthrin, which is marketed under the trade name Baythroid,[21] is the remarkable result of a programme directed at the synthesis of all seven possible compounds with fluorinated alcohol modifications.[22] In comparison to cypermethrin (**13**), cyfluthrin realized a more than threefold reduction in use rate for the control of cotton pests.[23] As a result of its long-lasting residual action and ingestion effect, cyfluthrin (**14**) is also recommended as a household insecticide for the control of houseflies, mosquitoes, or cockroaches. The launch of CF_3-containing pyrethroids started in the 1980s with λ-cyhalothrin (**15**; ICI/Zeneca)[24]. That this product represents the optimimum choice of fluorine-containing substituent for activity has been demonstrated by comparison with other possible fluorinated derivatives (Scheme 4). As a result of the presence of the CF_3 group, λ-cyhalothrin (**15**) also has effects on phytophagous mites. Six years after the launch of λ-cyhalothrin, bifenthrin (**16**)[25] was marketed as a broad-spectrum pyrethroid with excellent potential as a foliar insecticide and as one of the most important termiticides. Exploitation of the acidic part of λ-cyhalothrin (**15**) allowed tetra-



Scheme 4. *Launch of synthetic pyrethroids—fluorine introduction at the phenyl moiety (**14**, **17**) and trifluoromethyl introduction at the side chain (**15**–**18**).*

fluorobenzyl alcohol to be selected specifically and used to form a soil-applicable insecticide—the result was tefluthrin (**17**).[26] Replacement of the terminal vinyl halogen atom with a fluorine-containing ester group led to acrinathrin (**18**),[27] which was commercialized on the agricultural market as an insecticide and acaricide. Attracted by Bayer's success with cyfluthrin (**14**) and β-cyfluthrin (**19**; same structure as **14** but the technical grade contains a different proportion of diastereomers; see ref. [34]), others later incorporated the special substitution pattern of the 4-fluoro-3-phenoxy-benzyl substituent into several different active ingredients (Scheme 5), such as MTI 800 (**20**;



Scheme 5. *MTI 800 (**20**), protrifenbute (**21**), eflusilanate (**22**), and flumethrin (**23**).*

1982, Mitsui Toatsu)[28] and protrifenbute (**21**; 1987, FMC),[29] as well as into commercial products like silicon-containing eflusilanate (**22**; 1991, Bayer CropScience/Hoechst)[30] or flumethrin (**23**; 1979, Bayer CropScience)[31].

The more active form of cyfluthrin (**14**) for interaction at receptor sites involves a conformation in which the 3-phenoxy substituent is twisted because of the effect of the fluorine atom in the 4-position. This fact correlates well with the results obtained from a search of the Cambridge Structural Database (CSD) for the 3-phenoxy-benzyl fragment; from around 163 000 compounds, eight relevant X-ray structures were selected that fulfil the criteria within the substructure search regarding allocation of dihedral angles as a function of substituents in the *para*-position. However, it has to be pointed out that the crystal packing effect may have an influence on the X-ray structures outlined in Figure 3. In the insecticidally active compound **22** (Figure 3, magenta) the 3-phenoxy substituent is twisted because of electrostatic interaction between the fluorine atom in the 4-position and the 3-phenoxy aryl moiety. In the presence of a hydrogen atom in the 4-position, that is, in the compound containing only the 3-phenoxy-benzyl moiety, a statistically uniformly distributed conformation is observed (Figure 3, grey). A different orientation of the 4-chloro-3-phenoxy-benzyl moiety was observed (Figure 3, blue). There is a remarkable qualitative relationship between these structural findings and the observed insecticidal activity of these synthetic pyrethroids.

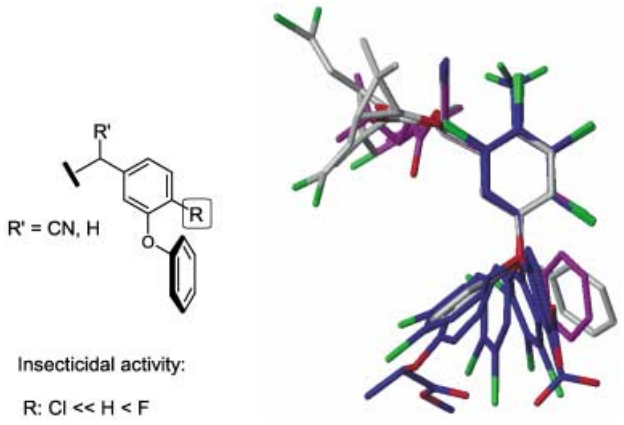
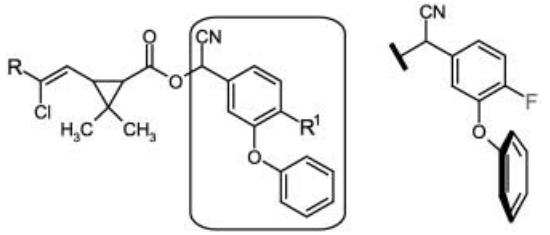


Figure 3. *Results of a search for the 3-phenoxy-benzyl fragment in the CSD. Magenta, 4-fluoro-3-phenoxy benzyl moiety; grey, H atom in the 4-position; blue, 4-chloro-3-phenoxy benzyl moiety; green, halogen; red, oxygen.*

A comparison of the physical and chemical environment-related properties of structurally similar pyrethroids (Table 1) demonstrates the influence of the fluorine atom at the phenyl moiety and the CF_3 group on the vinyl side chain. The data indicate that all pyrethroids have a high octanol/water partition coefficient. In comparison to other pyrethroids, cyfluthrin (**14**) has a lower affinity for soil or sediment particles. In aqueous solution, pyrethroids like cyfluthrin (**14**) are relatively stable at acid and neutral pH values but begin to hydrolyze readily under alkaline conditions. The pyrethroids vary in their susceptibility to light. Aqueous solutions of cyfluthrin (**14**) are fairly susceptible; cypermethrin (**13**) and cyhalothrin (**15**) not quite as susceptible. The relative insecticidal activity of established pyrethroids against houseflies compared with their relative mammalian toxicity to rats is depicted in Figure 4. The effi-

Table 1. *Summary of selected physical and chemical environmental properties of the pyrethroids (**13**–**15**).*[32]



Substituents R/R[1]	Cl/H (**13**)	Cl/F (**14**)	F_3C/H (**15**)
log *P*	6.54	5.97	7.00
Soil adsorption, K_{oc}	310 000	124 000	326 000
Hydrolysis half-life, *d*			
pH 5	619	stable	stable
pH 7	274	183	stable
pH 9	1.90	1.84	8.66
Photolysis half-life, *d*			
Water	30.1	0.673	24.5
Soil	165	5.02	53.7

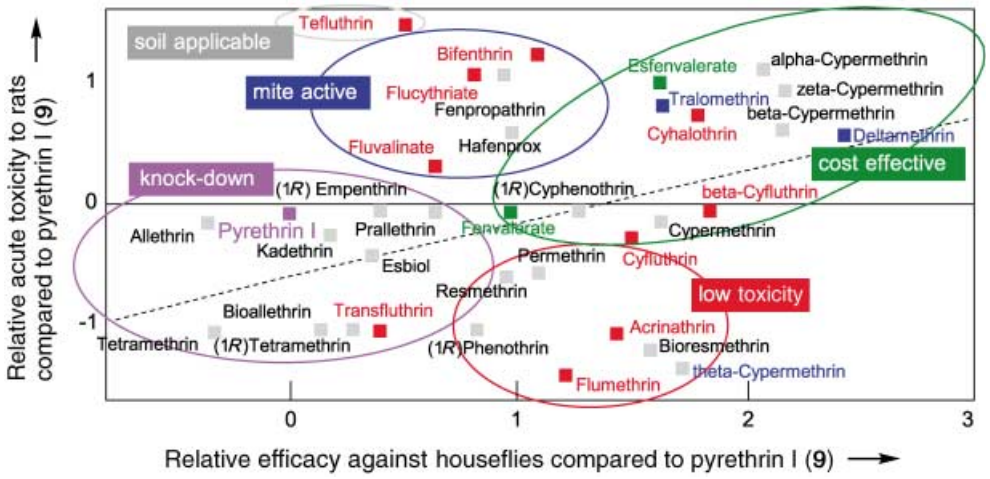


Figure 4. *Relative acute toxicity of established pyrethroids towards rats plotted against relative efficacy against houseflies, compared to pyrethrin I (**9**) in both cases.[33] See the main text for an explanation of the terms and color code used.*

cacy and toxicity relative to pyrethrin I (**9**) were calculated as the difference between the logarithmic LD_{50} value (LD_{50} = the dose that is lethal for 50% of test targets) of **9** and the corresponding value of the pyrethroid. In this manner, pyrethrin I (**9**) is made the zero point of the coordinate system and a pyrethroid found one division to the right and one division up from pyrethrin I (**9**) is ten times more effective and ten times more toxic to rats than is **9**. All pyrethroids colour coded red contain fluorine substituents. The figure shows that the pyrethroids form clusters of compounds close together in the graph. Accordingly, the pyrethroids can be separated into the following application areas:

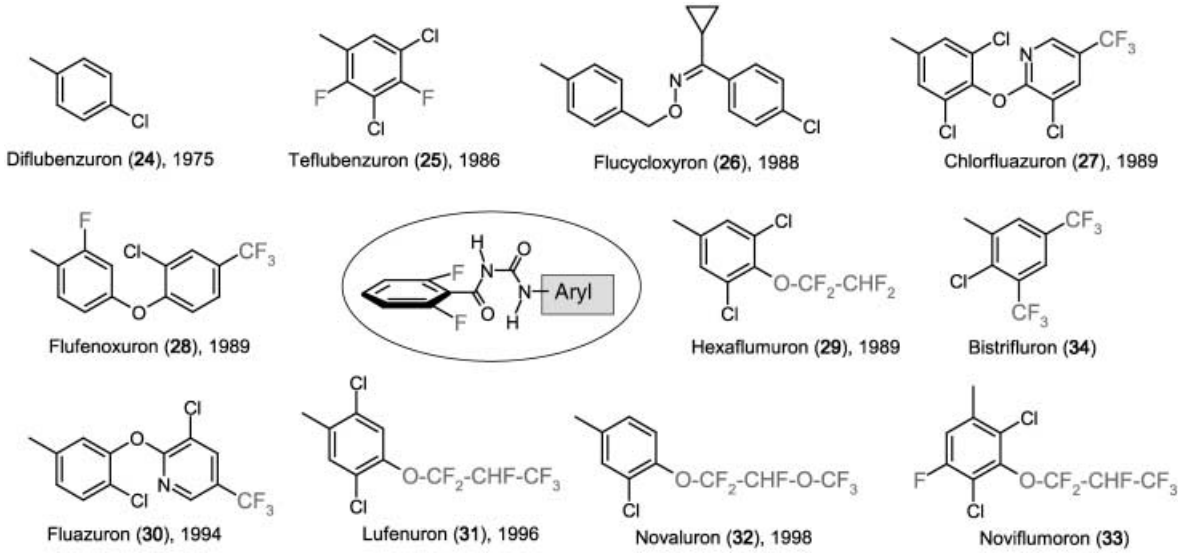
a) *Knock-down substances*: These compounds have a similar or slightly more potent lethal effect and better knock-down action than pyrethrin I (**9**) and are useful for indoor applications (see also, allethrin (**10**)).
b) *Soil-applicable substances*: Optimization of the volatility and water solubility of tetrafluorobenzyl analogues with extended half-lives in soil led to the discovery of tefluthrin (**17**), which is the most acutely toxic pyrethroid with moderate insecticidal activity.
c) *Mite-active substances*: These pyrethroids are noncyclopropane-type pyrethroids, except for bifenthrin (**16**) and acrinathrin (**18**). The miticide activity of these compounds is governed not only by direct toxic action, but also by the effects of the compounds on the behavior, reproduction, and development of mites.
d) *Low-toxicity substances*: These low-toxicity acutely acting pyrethroids have various alcoholic substituents, such as the 4-fluoro-3-phenoxy-benzyl group in flumethrin (**23**; see also, acrinathrin (**18**)). They are currently used for the control of household, public, and animal-health pests.
e) *Cost-effective substances*: These pyrethroids, like cyhalothrin (**15**) and β-cyfluthrin (**19**), are at least one order of magnitude more effective as insecticides and moderately more toxic to rats than pyrethrin I (**9**). The main application field of these compounds is in agriculture and they are efficient against a wide range of *Lepidoptera*, *Coleoptera*, *Homoptera*, and other pests. All of these compounds are 3-phenoxybenzyl derivatives substituted with an α-cyano group, which results in higher metabolic stability and strong intrinsic potency at the target site.

Up to now, 37 ester and three nonester-type pyrethroids are listed in The Pesticide Manual,[34] which contains all the currently used and registered active ingredients worldwide.

Insect growth regulators—*N*-benzoyl-*N*′-phenyl ureas

Over the past three decades, *N*-benzoyl-*N*′-phenyl ureas have been developed and used as commercial insect growth regulants (IGRs).[35] These compounds act on insects of various orders by inhibiting chitin formation and thereby causing abnormal endocuticular deposition and abortive molting.[36] The search for potent acyl ureas has led to the synthesis of numerous derivatives, such as diflubenzuron (**24**),[37] teflubenzuron (**25**),[38] flucycloxuron (**26**),[39] chlorfluazuron (**27**),[40] flufenoxuron (**28**),[41] hexaflumuron (**29**),[42] fluazuron (**30**),[43] and lufenuron (**31**),[44] and to the development of novel IGRs such as novaluron (**32**),[45] noviflumuron (**33**),[46] or bistrifluron (**34**),[47] which contain the typical *N*-2,6-difluorobenzoyl moiety.[48] In addition, the *N*′-arylamine part of these molecules contains fluorine in most cases, sometimes together with various types of fluorinated substituents, such as F_3C, $F_2HC{-}F_2C{-}O$, $F_3C{-}FHC{-}F_2C{-}O$, or $F_3C{-}O{-}FHC{-}F_2C{-}O$. The introduction of an electron-withdrawing substitution pattern often extended the pesticidal spectrum to include mites and ticks (Scheme 6).

Benzoyl ureas have some of the most unusual physical properties of any of the active ingredients used in crop protection. These ureas are all highly crystalline, lipophillic solids with high melting points. Consequently, the compounds have extremly low vapour pressure and very low water solubility. These properties result in both advantages and disadvantages for crop

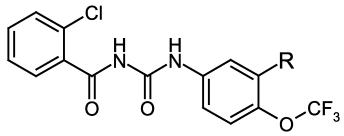


Scheme 6. *N-2,6-Difluorobenzoyl-N′-phenyl ureas—various commercial products.*

protection use with regard to toxicological behavior, ease of formulation, and interaction with the environment.

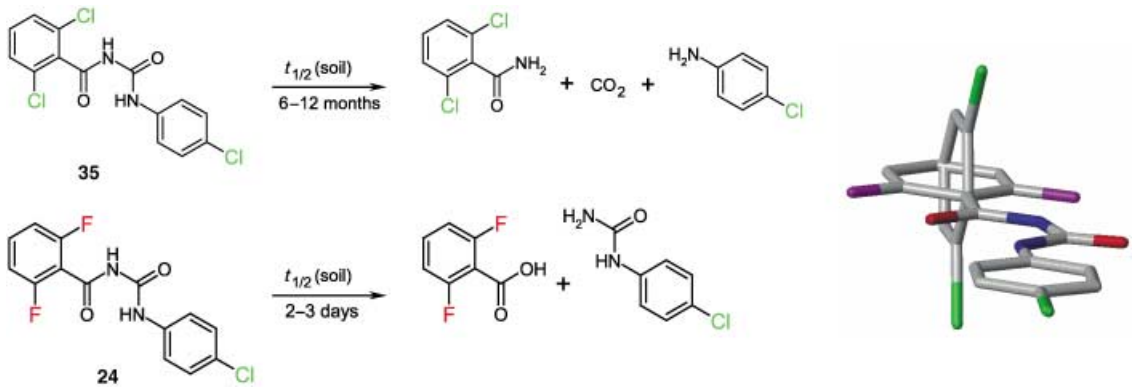
The beneficial steric effects of both the fluorine atom in the 2-position and that in the 6-position on the inhibition of chitin synthase,[49] and the difference in environmental stability factors such as soil degradation half-life caused by the presence of these atoms have already been discussed for **24**, which has a half-life of around three days under alkaline conditions (Scheme 6).[50] The chemical and metabolic degradation of these ureas has been outlined by Roberts and Hutson.[51] The *N*-2,6-difluorobenzoyl-*N′*-phenyl ureas are stable at acidic pH values but are hydrolyzed at pH 9–10 to give 2,6-difluorobenzoic acid and a phenyl urea. In contrast to the conformation of the corresponding and less active 2,6-dichloro-benzoyl derivative **35**, which degrades in between six and twelve months, the 2,6-difluoro-benzoyl moiety in **24** is in-plane with the whole urea structure. As a consequence, different metabolic pathways are observed for these two compounds (Scheme 7).

During the chemical optimization of insecticidal triflumuron (**36**; 1979, Bayer Crop Science)[52] analogues with activity against coleoptera pests like *Phaedon cochleariae*, the *N*-2-chlorobenzoyl moiety (R = Cl) was selected by Bayer researchers for further study (Scheme 8). Some of the most successful substitutions include the use of F_3C and F_3CO groups as so-



Scheme 8. *Triflumuron (**36**) and its derivative **37**.*

called pseudohalogens. Variation of the *N′*-phenylamine moiety with this fact in mind revealed that, in this case, 2,3,5-F_3, 4-F_3C, and 2,3-F_2, 4-F_3C substitution patterns are most favorable. These derivatives show good activity against *P. cochleariae* down to 0.1 ppm. Furthermore, benzoyl ureas containing *N′*-phenylamine moieties of type F and G (Figure 5) with fluorine

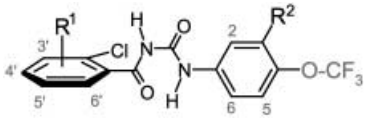


Scheme 7. *Soil degradation of N-benzoyl-N′-phenyl ureas—the effect of fluorine substituents.*

atoms in the 2,3 and 2,3,5-positions show good activity against two different lepidopteran pests, *Spodoptera frugiperda* and *Plutella xylostella*, down to 0.01 ppm.

During the further optimization of the *N*′-phenylamine moiety, an F_3CO residue in the 4-position was found to be beneficial (Figure 5). The most active benzoyl urea is derivative **37**, which has a 3-Cl-4-F_3CO substitution pattern in the *N*′-phenylamine moiety. Introduction of one fluorine atom at the 5′ or 6′-position together with an additional substituent such as an F_3C or F_3CO residue in the 3-position strongly influences the selectivity for both coleopteran and lepidopteran pests, such as *P. cochleariae* and *P. xylostella*. A summary of the results obtained is shown in Table 2. Interestingly, when the fluorine atom was shifted from the 5′ to the 6′-position in the 2′-chlorobenzoyl moiety, the resulting 3-F_3C-4-F_3CO-phenylamine derivative **38** was found to have 100-fold and 10-fold better activities against the coleopteran and lepidopteran pests, respectively, than the corresponding 3,4-bis(trifluoromethoxy)-phenylamine derivative **39**. Finally, triflumuron (**36**) was launched as Alsystin by Bayer CropScience. This compound has a broad insecticidal activity combined with a strong feeding and contact action and is especially active against biting insect pests like *S. frugiperda* (active down to 0.064 ppm) and *P. cochleariae* (active down to 8 ppm).[53] Since it is not toxic to vertebrates, triflumuron (**36**) is also used in veterinary medicine as Starycide, and in the home against fleas and cockroaches as Baycidal.

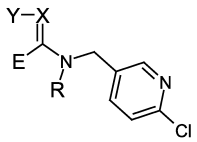
Table 2. *Summary of the effect of fluorine substituents in the* N′*-phenylamine moiety on insecticidal activity (LD_{95} in ppm) against coleopteran and lepidopteran pests.*



R^1	R^2	*P. cochleariae*	*P. xylostella*
5′-F	CF_3	> 1000	1000
5′-F	OCF_3	> 1000	1000
(**38**) 6′-F	CF_3	10	1.0
(**39**) 6′-F	OCF_3	1000	10

Neonicotinoids

Neonicotinoids such as imidacloprid (**40**; 1991, Bayer CropScience)[54], nitenpyram (**41**; 1996, Takeda),[55] or acetamiprid (**42**; 1996, Nippon Soda)[56] are increasingly used worldwide as a novel class of chloronicotinyl insecticides (CNIs; Scheme 9).



(**40**) X-Y: =N-NO_2; R-E: CH_2-CH_2-NH
(**41**) X-Y: =CH-NO_2; R: Et; E: NH-Me
(**42**) X-Y: =N-CN; R, E: Me

Scheme 9. *Imidacloprid (**40**), nitenpyram (**41**), and acetamiprid (**42**).*

These agonists act selectively on the nicotinic acetylcholine receptors[57] of insects and are part of a single mode of action group, as defined by the Insecticide Resistance Committee for pest management purposes. The excellent insecticidal activity of imidacloprid (**40**; R = H) was achieved by coupling a special heterocyclic group, the 6-chloro-pyrid-3-yl-methyl residue, to a 2-(*N*-nitroimino)-imidazolidine building block.[58] However, the CNIs also display different types of pharmacophores, such as nitroguanidine [N–C(N)=N–NO_2], nitroenamine [N–C(N)=CH–NO_2], and N-cyanoamidines [N–C(Me)=N–CN]. The introduction of fluorinated pyrid-3-yl-methyl moieties resulted in insecticidal activity against sucking insects.

The activity of a substance I towards inhibition of an enzymatic reaction can be approximately evaluated as the index

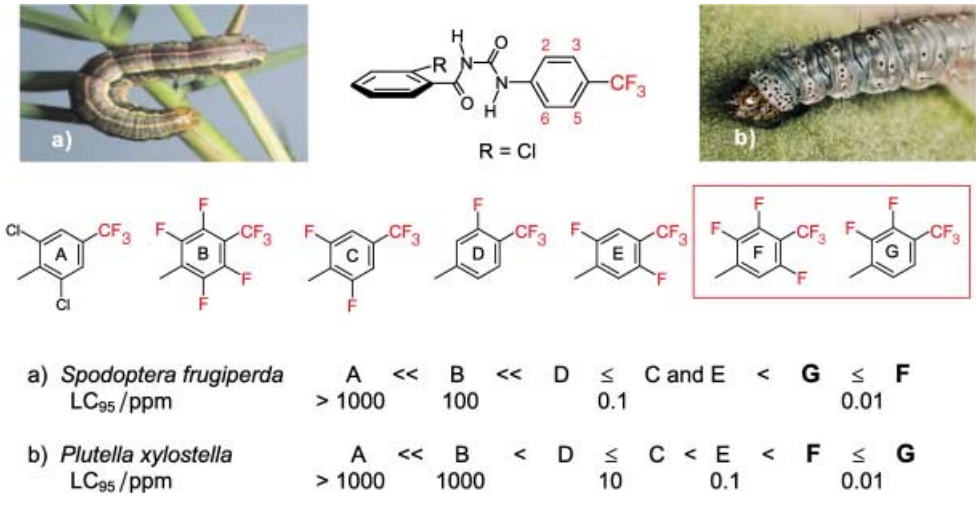


Figure 5. *Structure–activity relationship (SAR) of* N*-2-chloro-benzoyl-*N′*-4-trifluoromethylphenyl ureas—effect of fluorine substituents.*

pI_{50} (I_{50} = quantity of I required for 50% inhibition).[59] The 5-chloro-5-fluoro-pyrid-3-yl moiety has the same pI_{50} value (9.1) as imidacloprid (**40**), combined with a good activity against *Myzus persicae*, whereas the 5-chloro-2-fluoro-pyrid-3-yl moiety has a somewhat lower pI_{50} value (8.3) than **40** and is strongly active against *Aphis fabae*. To clarify this effect, the differences in hydrogen bond acceptance by the pyridyl nitrogen atom were modeled by first principles quantum chemical calculations. Quantum chemical calculations for imidacloprid (**40**) and all the fluorinated imidacloprid derivatives optimized by high-level density functional theory calculations[60] have shown that the geometries of imidacloprid (**40**) and its 6-chloro-5-fluoro analogue are somewhat different from that of the 6-chloro-2-fluoro-analogue (Figure 6).

Kagabu[61] described the structure–activity relationship of pyridylmethyl-substituted 2-nitromethylene imidazolidines **43**–**47** (Figure 7). Generally, the insecticidal activity against the green rice leafhopper *Nephotettix cincticeps* increases with the introduction of a halogen atom at the 6-position of the pyridine ring. Whereas a CF_3 group in the 6-position (**44**) did not enhance activity compared to that achieved with a hydrogen atom as the substituent (**43**), the 6-bromine derivative (**45**) is more active than **43** and **44** by a factor of 5. Exchange of the atom in the 6-position for chlorine or fluorine leads to the equally potent compounds **46** and **47**, which show strong activity down to 0.32 ppm, as outlined in Figure 7.

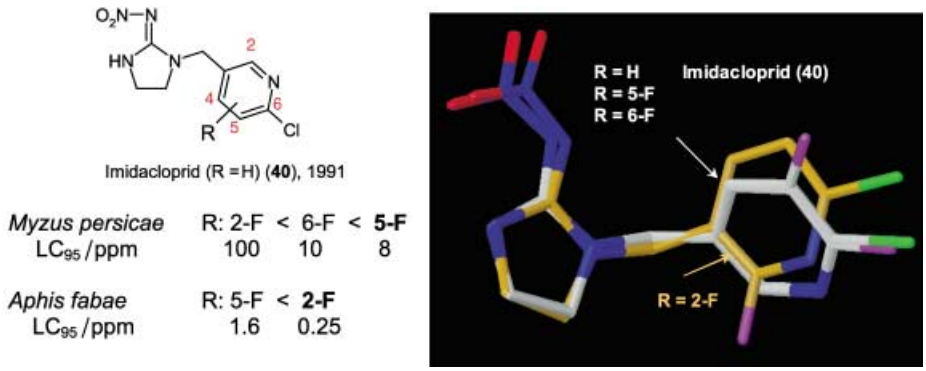


Figure 6. *Insecticidal activity and the effect of fluorine on geometries optimized by high-level density functional theory calculations. The structure of the 6-chloro-5-fluoro-pyrid-3-yl analogue is white and that of the 6-chloro-2-fluoro-pyrid-3-yl analogue is yellow.*

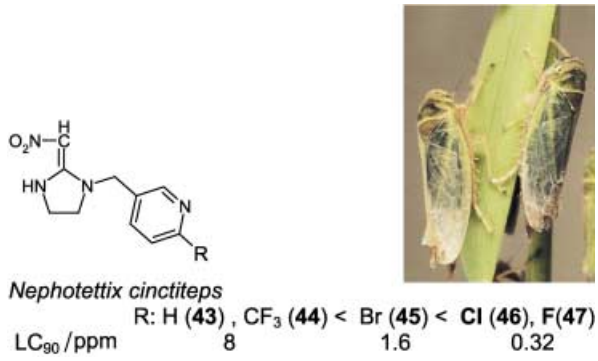


Figure 7. *2-Nitromethylene-imidazolidines **43**–**47**.*

The effect of halogen-substituted hetaryl moieties in different nitenpyram derivatives (**48**–**51**) has been described by Takeda. Surprisingly, in this case the insecticidal activities of the 6-bromine (**50**), 6-chlorine (**41**, nitenpyram), and 6-fluorine (**51**) derivatives against the brown planthopper are all the same (LD_{95} = 0.5 ppm). However, the efficacy of these compounds is a factor of 5 and a factor of 80 better than the efficacies of the corresponding 6-methylpyridyl (**49**) and pyridyl derivatives (**48**), respectively. From the geometries of CNIs shown in Figure 6, hydrogen-bonded complexes with water were constructed and these structures were treated in the very same way as the CNI geometries. The difference between the relative free energy of the free molecule and that of the molecule embedded in a dielectric was chosen as a model parameter for the quantification of the hydrogen-bonding properties of the pyridyl nitrogen atom. A correlation could be established between the observed insecticidal activity of nitenpyram analogues **48**–**51** (Figure 8) against the brown planthopper and the hydrogen-bonding properties of the pyridyl nitrogen atoms.

The insecticidal activity of halogen-containing acetamiprid derivatives **52**–**53** (Scheme 10) against sucking insects has been described by Nippon Soda scientists. It was found that the incorporation of fluorine into the *N*-methyl side chain leads to a compound (**53**) is as potent against *Aphis gossypii* as the

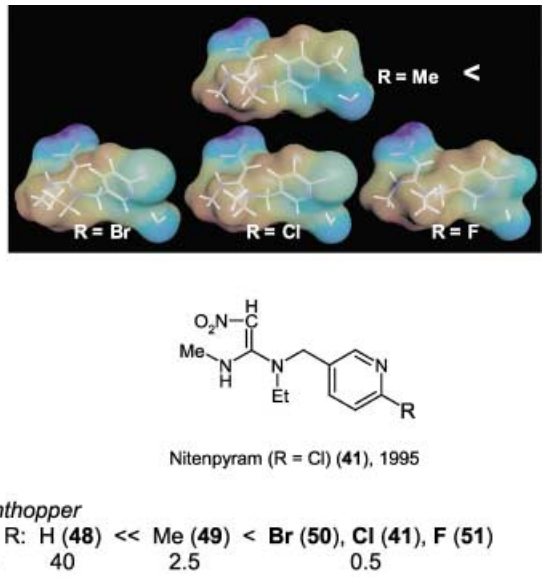
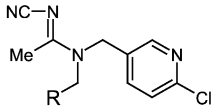


Figure 8. *Insecticidal activity and the effect of fluorine on the geometries of nitenpyram derivatives. Geometries were optimized by high-level density functional theory calculations. See the main text for more details.*



Aphis gossypii (spraying method, 1st instar nymphs)

	R: Cl (**52**)	<	**F** (**53**)	≅	**H** (**42**)
LC_{50}/ppm	1.5		0.058		0.056

Plutella xylostella (leaf-dipping method, 2nd instar larvae)

	R: Cl (**52**)	<	F (**53**)	<	**H** (**42**)
LC_{50}/ppm	> 500		73		19

Scheme 10. *Halogen-containing acetamiprid derivatives **52** and **53**.*

parent compound **42**, whereas the *N*-chloromethyl derivative **52** is weaker by a factor of about 25. Application of these compounds against lepidopteran pests revealed the following trend for insecticidal activity against *P. xylostella*: *N*-methyl (**42**, acetamiprid) > *N*-fluoromethyl (**53**) ≫ *N*-chloromethyl (**52**).

Difluorination at the *N*-cyanoiminoacetyl group leads to a general decrease in activity against both insect species. The molecule–water complexes of acetamiprid derivatives **52**–**53** were modeled in the same way as described above for **48**–**51**. Quantification of the hydrogen-bonding properties of the pyridyl nitrogen atoms gave results closely related to the observed trend in insecticidal activity against *A. gossypii*.

4. Fungicides Containing Fluorine

Azoles

The triazole fungicides represent one of the most important chemical groups of widely used agrochemicals.[62] The main mode of action of these compounds is inhibition of the cytochrome-P_{450}-dependent demethylation of an intermediate (at the C_{14}-methyl group of lanosterol or of C_{24}-methylene-$C_{24,25}$-dihydrolanosterol) in the sterol biosynthesis pathway in fungi.[63] The majority of these so-called demethylation inhibitors (DMIs)[64] undergo systemic movement within plants. The systemic properties of individual DMIs, reflected in part by their log *P* values, are of relevance in the control of particular plant diseases. The number of DMI fungicides introduced as commercial products over the past three decades exceeds 30. Within the azole derivatives launched between the years 1974 and 1994, the chlorophenyl moiety is very common, possibly because of the favorable physicochemical properties obtained through its use, such as an advantageous log *P* value. The chlorophenyl moiety is present in nearly 74% of these azoles.[65] Nevertheless, 18.5% of the azoles commercialized so far possess fluorine or fluorine-containing substituents. Prominent examples are flutriafol (**1**; Syngenta),[66] flusilazole (**54**; DuPont),[67] tetraconazole (**55**; Sumitomo),[68] epoxiconazole (**56**; BASF),[69] and fluquinconazole (**57**; Aventis; Scheme 11)[70].

A comparison of the systemic broad-spectrum fungicide tebuconazole (**58**, R = Cl, R′, R″ = H, Figure 9)[71], tradename Folicur, with its fluorinated analogue (**59**, R = F, R′, R″ = H) demonstrates that both have practically the same plant compatibility and activity against *Venturia inaequalis* (nearly the same, see Figure 9) and *Botrytis cinerea*. However, mono- or difluorination

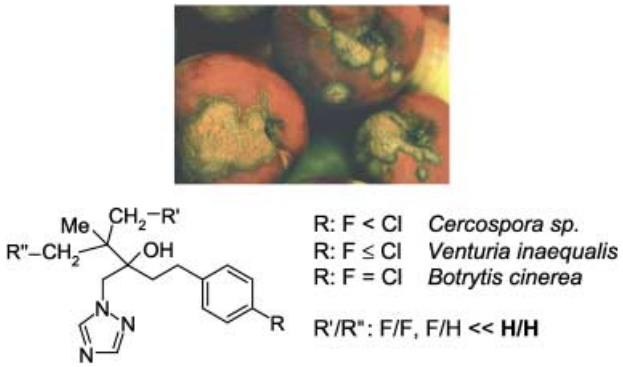
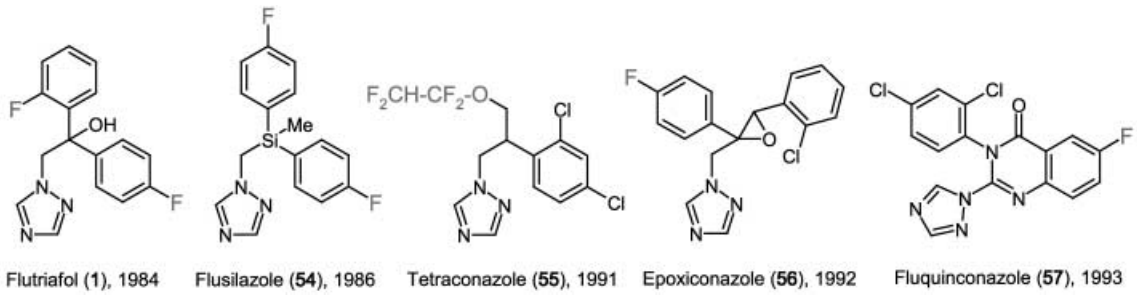


Figure 9. *Fluorinated analogues of tebuconazole (**58**).*

of the tertiary butyl side chain (R′/R″ = F/H, F/F) leads to a decrease in activity against these specific fungi. Cyclohexyl-containing triazole fungicides (e.g. **60**) show weak activity as plant growth regulators (PGRs; Figure 10). The fungicidal activity increases upon incorporation of the halogens chlorine and fluorine into the *tert*-butyl side chain. Interestingly, introduction of a difluoro-*tert*-butyl side chain (R/R′ = H/F) leads to a highly active rice fungicide (**61**) with good efficacy against the important rice disease *Pyricularia oryzae*.

Plant growth regulators—pyrimidines as azole analogues

Some of the triazoles,[72] for example **60**, and especially bioisosteric pyrimidine analogues such as ancymidol (**62**, acute oral toxicity for rats: LD_{50} = 4500 mg kg^{-1}; Eli Lilly)[73] exhibit PGR ac-



Scheme 11. *Launch of fluorine-containing triazole derivatives **1**, **54**–**57**.*

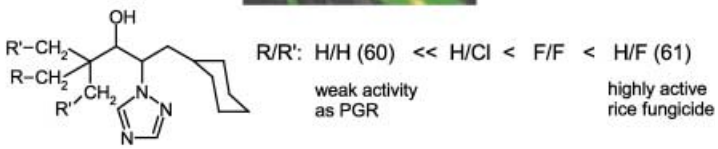
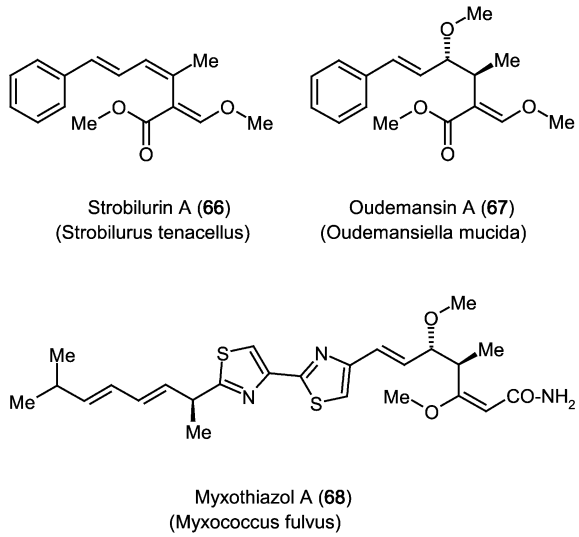


Figure 10. *Cyclohexyl-containing triazole fungicides **60** and **61**.*

tivity in a wide range of mono- and dicotyledonous species and act by reducing internodal elongation through interaction with the gibberellin biosynthesis pathway.[74] Replacement of the methoxyphenyl group with a trifluoromethoxyphenyl moiety, and the cyclopropyl group with isopropyl (as in flurprimidol (**63**), $LD_{50} = 709\ mg\,kg^{-1}$; Dow AgroScience)[75] leads to an increase in the acute toxicity for rats (Scheme 12). Replacement of the 4-chlorophenoxy group in **64** with a 4-fluorophenoxy moiety (**65**) gives an increase in PGR activity.[76]

Strobilurins

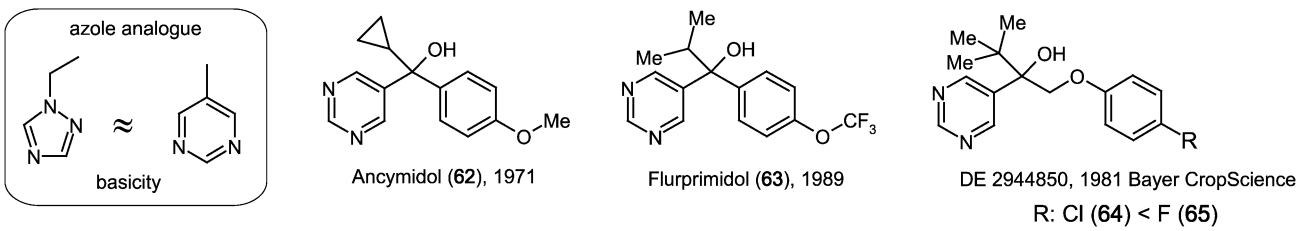
The discovery of strobilurins, an important class of agricultural fungicides, was inspired by a group of natural fungicidal derivatives of β-methoxyacrylic acid, the simplest of which are strobilurin A (**66**),[77] oudemansin A (**67**),[78] and myxothiazol A (**68**; Scheme 13).[79] Owing to their common structural feature, this group of compounds was named the β-methoxyacrylates. Sales of strobilurin and related fungicides totalled approximately US$ 620 million in 1999. This figure represents over 10% of the global fungicide market, which is an outstanding achievment within just four years of the first sales. Like oudemansins and myxothiazoles,[80] all strobilurins inhibit mitochondrial respiration by binding the so-called Q_o site of cytochrome *b*.[81] Cytochrome *b* is part of the cytochrome bc_1 complex,[82,83] which is located in the inner mitochondrial membrane of fungi and other eukaryotes.[84] The strobilurines bind reversibly at a specific site on cytochrome *b*. The β-methoxyacrylates are composed of three parts, as shown in Scheme 14a–c. The companies ICI (now Syngenta) and BASF filed the first patent applications for β-methoxyacrylates in 1984/1985 and launched the commercial products azoxystrobin (**69**)[85] and kresoxim-methyl (**70**)[86] in 1996. Three years later, metominostrobin (**71**)[87] was launched by Shionogi. Up to this



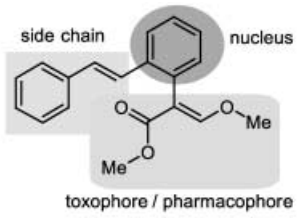
Scheme 13. *Strobilurin A (**66**), oudemansin A (**67**), and myxothiazol A (**68**).*

time, none of the three marketed compounds contained a halogen. However, the fungicide trifloxystrobin (**72**),[88] tradename Flint (Bayer's aquisition from Syngenta in December 2000), contains a CF_3-phenyl moiety in its side chain and belongs to a new generation of strobilurin fungicides (Scheme 15). Like kresoxim-methyl (**70**, vapour pressure: 2.3×10^{-3} mPa at 20 °C), trifloxystrobin (**72**, vapour pressure: 3.4×10^{-3} mPa at 25 °C) delivers disease control in the vapour phase.[89] However, the strong affinity of **72** for wax makes the compound stick to the upper surfaces of plants for a long time, which leads to the formation of a rain-resistant store of the active ingredient. Redistribution mechanisms also help the compound to reach nearby areas that were not touched directly by the spray. For instance, trifloxystrobin (**72**) diffuses into the leaf tissue, from where it exerts a translaminar action. Smaller but still biologically effective amounts evaporate and are transported to other parts of the treated plant. This process means that the protective fungicidal coating that surrounds the plant and effectively wards off fungal infections is replinished from the store. Trifloxystrobin (**72**) shows an outstanding activity agains, for example, apple scab because of its inhibitory effects on multiple stages of the life cycle of *V. inaequalis*.

Fluoxastrobin (**73**; Figure 11)[90] is a leaf-systemic broad-spectrum strobilurin fungicide from the chemical class of dihydrodioxazines currently being developed by Bayer CropScience for use mainly on cereal crops. This novel derivative provides both



Scheme 12. *Plant growth regulators—pyrimidines as azole analogues.*

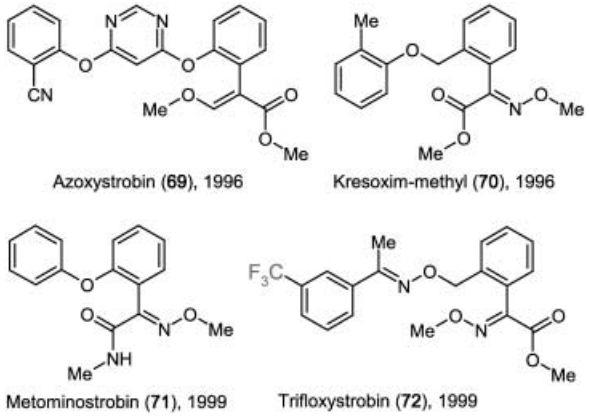


a) the ***toxophore*** or ***pharmacophore*** is essential for biological activity

b) the ***side chain*** is necessary for optimal lipophilicity and can be modified within a broad chemical range

c) the ***nucleus*** connects the toxophore with the side chain.

Scheme 14. *Structural elements of synthetic β-methoxyacrylates.*



Scheme 15. *Commercialized strobilurines **69–71** and flint (**72**).*

a rapid initial effect and prolonged activity as a result of its protective and leaf-systemic properties. The excellent leaf systemicity is the basis for rapid uptake and even, acropetal distribution of the active ingredient in the leaf. The very good plant compatibility of the compound means its penetration through the cuticle into the leaf can be optimized further by using suitable formulation types. SARs indicate that the fluorine atom has a beneficial effect on the phytotoxicity and leaf systemicity of this novel fungicide. In contrast to its very high leaf systemicity, the uptake of fluoxastrobin (**73**) through seeds and roots is relatively slow, as demonstrated by tests with [^{14}C]-radiolabeled compounds (Figure 11).

Seed treatment with fluoxastrobin (**73**) provides both very good broad-spectrum control and long-lasting protection of the young seedling from seed and soil-borne pathogens. Applied as a foliar spray in cereals, **73** provides excellent control of, for example, *Septoria* leaf spot (*Septoria tritici*), *Septoria* leaf and glume blotch (*Leptosphaeria nodorum*), rusts (*Puccinia recondita, P. striiformis, P. hordei*), *Helminthosporium* diseases in wheat and barley, and scald and powdery mildew. As a contribution to an antiresistance management strategy for strobilurins, fluoxastrobin (**73**) will either be developed as a coformulation or recommended as a tank mix with fungicides from other chemical classes. Mixtures of fluoxastrobin (**73**) with selected fungicides from Bayer CropScience, such as the new broad-spectrum fungicide and DMI prothioconazole, tradename Fandango (Bayer CropScience),[91] result in all-round improved control of diseases such as *Pseudocercosporella* and *Fusarium* ear blight.

An indication shift from fungicidally to acaricidally active β-methoxyacrylate strobilurins is achieved by exchange of the 6-trifluoromethyl-pyrid-2-yl moiety in the picoxystrobin (**74**; 2002, Syngenta)[92] side chain with a 2-isopropoxy-6-trifluoromethyl-pyrimid-4-yl moiety (**75**; Nippon Soda, BASF; Scheme 16).[93] Compounds with the latter side chain show acaricidal activity against *Panonychus ulmi* and *Tetranychus urticae* on citrus fruit and apples, as well as against spider mites on pears.

5. Herbicides Containing Fluorine

Cereals, alongside maize, rice, and soybeans, are among the major crops that form the greater part of the diet of the global population. Herbicides are and will remain an essential production factor if the continously increasing demand for cereals throughout the world is to be satisfied. Bayer CropScience is the market leader in this field as a result of continuous research efforts and the launch of a series of new active ingredients that have consistently offered farmers progressive solutions for weed management in cereals since the early 1950s. More than 70% of the Bayer-owned herbicides contain halogens (Table 3). Excellent efficacy, selectivity, and plant compatibility are the most prominent advantages of the fluorine-containing commercial products.

Inhibitors of carotenoid biosynthesis

Most of the commercial so-called bleaching herbicides[94] inhibit the synthesis of carotinoids by interfering with carotinoid

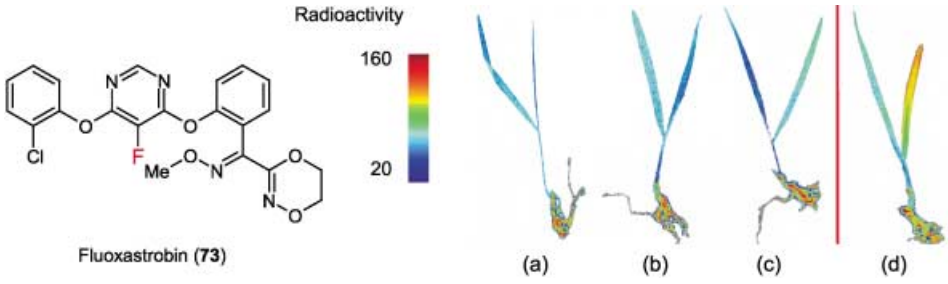
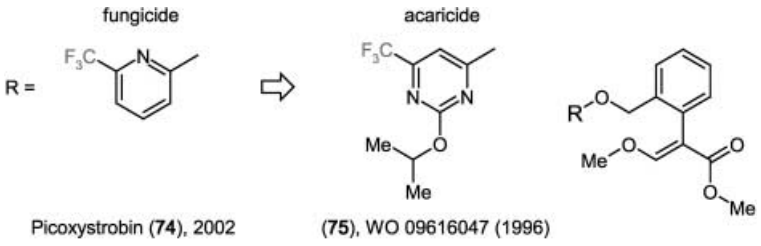


Figure 11. *Root systemicity—uptake and redistribution of [^{14}C]-fluoxastrobin (**73**) 2 days (a), 5 days (b), and 9 days (c) after root application, in comparison to uptake of [^{14}C]-tebuconazole (**58**) 9 days after application in the same way (d).*



Scheme 16. *Picoxystrobin (**74**) and the 2-isopropoxy-6-trifluoro-methyl-pyrimid-4-yl moiety (**75**).*

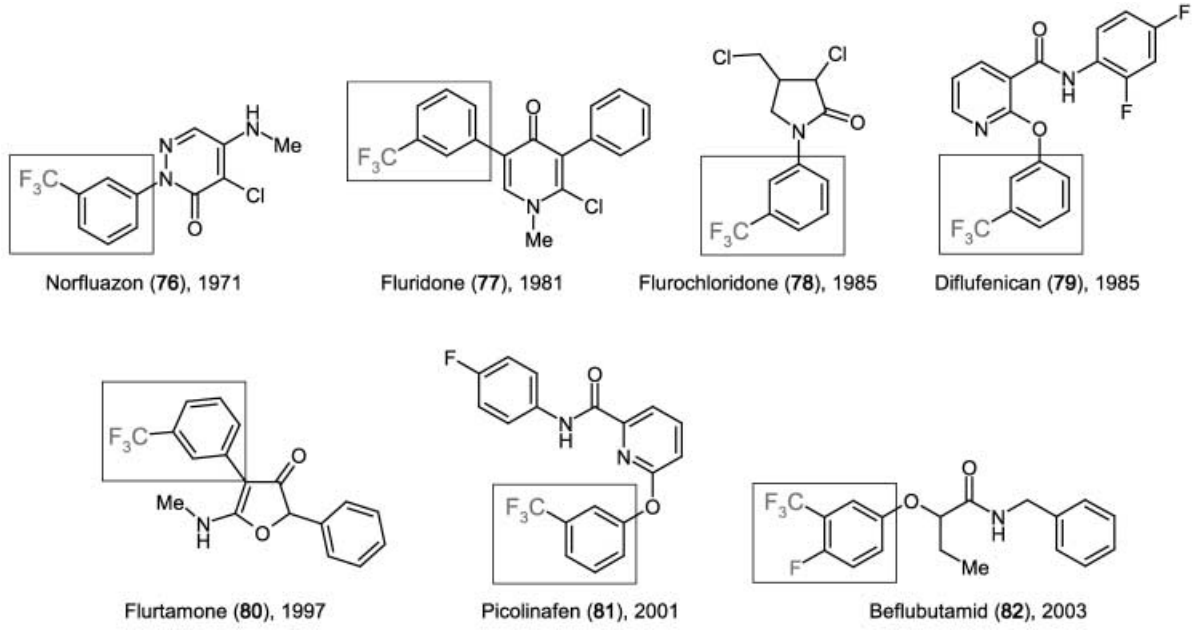
Table 3. *Milestone cereal herbicides from Bayer CropScience AG.*

Brand	Launch	Active ingredients	Halogen
2,4 D, MCPA	1950	Hormones	Cl
Actril/Oxytril	1967/1971	Ioxynil/Bromoxynil	I/Br
Arelon/Tolkan flo	1974	Isoproturon	
Illoxan, Hoelon, Hoegrass	1976	Diclofop	Cl
Tolkan Fox, Foxpro, Foxtar	1983	Bifenox	Cl
Quartz, **Javelin**, **Fenikan**, **First**, **DFF**	**1987**	**Diflufenican**	**F**
Puma S, Ralon S, Cheetah, Wildcat	1988	Fenoxaprop	Cl
Gratil, Eagle, Hoestar	1991	Amidosulfuron	
Bacara	**1997**	**Flurtamone**	**F**
Herold, **Axiom**	**1997**	**Flufenacet**	**F**
Hussar, Sekator, Chekker	1999	Iodosulfuron	I
Everest	**2000**	**Flucarbazon**	**F**
Attribut, Olympus	2001	Propoxycarbazon	
Atlantis, Cossack	2001	Mesosulfuron	

biosynthesis at the level of phytoene desaturase. The mode of action of these herbicides was reviewed a few years ago.[95] The enzyme kinetics of phytoene desaturase in the presence of several different inhibitors revealed reversible binding of the inhibitors to the enzyme and noncompetitive inhibition. Numerous relevant chemical classes of compounds have now been described (Scheme 17). A common substituent in most of the phytoene desaturase inhibitors is the 3-trifluoromethylphenyl moiety shown in norflurazon (**76**),[96] which is used for pre-emergence control of annual grasses and broad-leaved weeds, fluridone (**77**),[97] a selective water herbicide with activity against aquatic plants, and fluorochloridone (**78**),[98] a herbicide used for pre- and post-emergence control in maize, as well as in cereals and cotton. It is still not known which structural elements are essential to make a phytoene desaturase inhibitor potent at its target site. Nevertheless, the presence of the F_3C group in the *meta* position of the phenyl ring system in various substance classes of inhibitors reflects the essential properties of this moiety: high lipophilicity and an electron-withdrawing nature. Furthermore, there are strict requirements for substitution at the 5- or 6-membered heterocycle of the inhibitor, especially at the position most distant from the carbonyl group. Other commercial products are diflufenican (**79**),[99] which shows good selectivity as a pre- and post-emergence herbicide in winter wheat and barley, flurtamone (**80**),[100] applied in cereals as a mixture with diflufenican (**79**), and picolinafen (**81**),[101] which contains a pyridine skeleton similar to that of **79**. The novel selective herbicide for weed control in cereals, beflubutamid (**82**; Ube),[102] contains a 4-fluoro-3-trifluoromethylphenyl moiety.

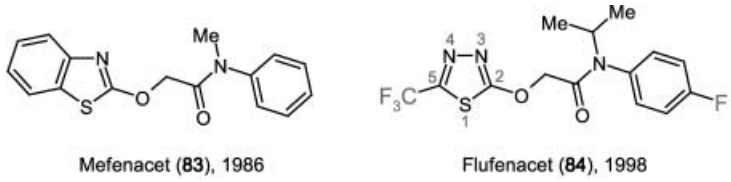
Oxyacetamides

Mefenacet (**83**; Hinochloa, 1986),[103] a selective inhibitor of cell growth and cell division, was the first commercial herbicide of the Bayer-owned oxyacetamide group and is used to control



Scheme 17. *Launch of synthetic inhibitors (**76**–**82**) of carotenoid biosynthesis.*

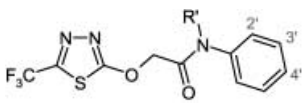
barnyard grass in irrigated paddy rice (Scheme 18). The intensive search for an oxyacetamide with efficacy as a herbicide even in the absence of irrigation water that can be used on maize, soybeans, and other crops led to the development of



Scheme 18. *Mefenacet (**83**) and flufenacet (**84**).*

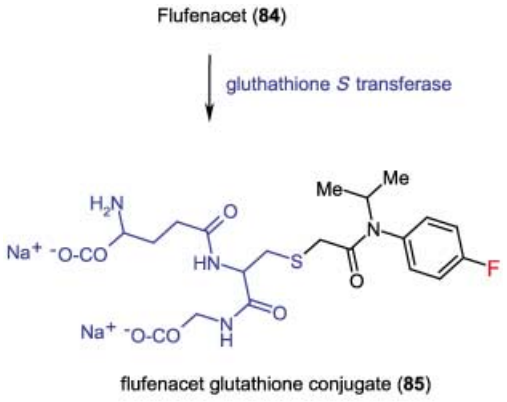
flufenacet (**84**; Axiom, 1998).[104] This compound has a weed control spectrum similar to that of chloroacetamide herbicides[105] and can be used to control a wide range of annual grass weeds, sedges, and some small-seeded broadleaf weeds. Flufenacet (**84**) introduced a new mode of action for the control of species of blackgrass that are resistant to acetyl coenzyme A carboxylase inhibitors[106, 107] and is an excellent mixing partner for other broadleaf herbicides. Finally, flufenacet (**84**) is a good example of a product that demonstrates the unique role of fluorine in the design of modern herbicides. The herbicidal activity, selectivity, and compatibility of this substance class was optimized on the basis of SAR correlations. It was found that not only the hetaryl moiety (e.g. activity with 1,3,4-oxadiazole < activity with 1,3,4-thiadiazole), but also the hetaryl substituent in the 5-position (Cl < F_2HC < F_3C) has a strong influence on herbicidal activity. In addition, the herbicidal selectivity and compatibility can be strongly influenced by the phenylamide part of the molecule. Comparison of different 2-phenylamide-substituted 5-trifluoro-1,3,4-thiadiazoles with respect to their efficacy and maize compatibility has shown that *N*-isopropyl is the most favorable substituent. The phenyl substitution pattern is important too. Whereas the unsubstituted phenyl moiety gives a good herbicidal activity against *Echinochloa crus galli*, the selectivity achieved is insufficient for soybeans and maize. By incorporating halogens like chlorine or fluorine, the selectivity of the oxyacetamides was significantly increased, but in the case of chlorine this improvement is correlated with reduced herbicidal activity. In addition, the three isomeric fluorophenylamides were investigated in order to identify the right position of fluorine in the phenyl moiety. Only the 4-fluorophenyl-containing compound **84** (R′ = *i*Pr, C-4′ = F; see Table 4, line 6) showed good herbicidal efficacy and selectivity against grasses, combined with suitability for use in maize and soybeans when applied pre-emergence at 125 g a.i./ha (greenhouse; Table 4). Herbicide selectivity is a major factor in agricultural weed control and results from the different detoxification abilities of plant species. The selectivity of important herbicides like atrazine (Zeazin, 1957),[108] alachlor (Lasso, 1966),[109] metolachlor (Dual, 1975)[110] and others originates from their covalent linkage to glutathione. Investigations on the metabolism of flufenacet (**84**) in immature maize and soybean seedlings exposed to C^{14}-labeled **84** showed that conjugation with glutathione is also the first step in the degradation pathway of this product. The activity of glutathione *S* transferase from maize seedlings towards flufenacet (**84**) is three to four times higher than the activities of the enzymes from other crops and weeds. The chemical structure of the flufenacet glutathione conjugate **85** (Figure 12)[111] demonstrates that that

Table 4. *Herbicidal activity [%] and compatibility [%] of oxyacetamides applied pre-ermergence at 125 g a.i./ha[a] (greenhouse).*



R′	C-2′	C-3′	C-4′	*Echinochloa crus-galli*	Soybean	Maize
Me	H	H	H	90	6	36
*i*Pr	H	H	H	93	2	15
*i*Pr	H	H	Cl	75	0	0
*i*Pr	H	Cl	H	90	0	0
*i*Pr	Cl	H	H	80	0	20
***i*Pr**	**H**	**H**	**F**	**95**	**0**	**0**
*i*Pr	H	F	H	90	0	15
*i*Pr	F	H	H	90	0	35

a.i., active ingredient.



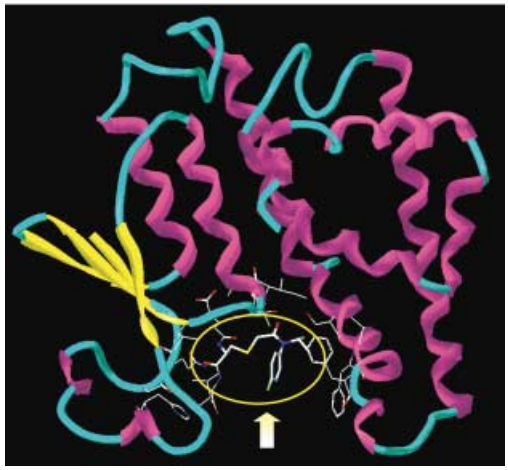
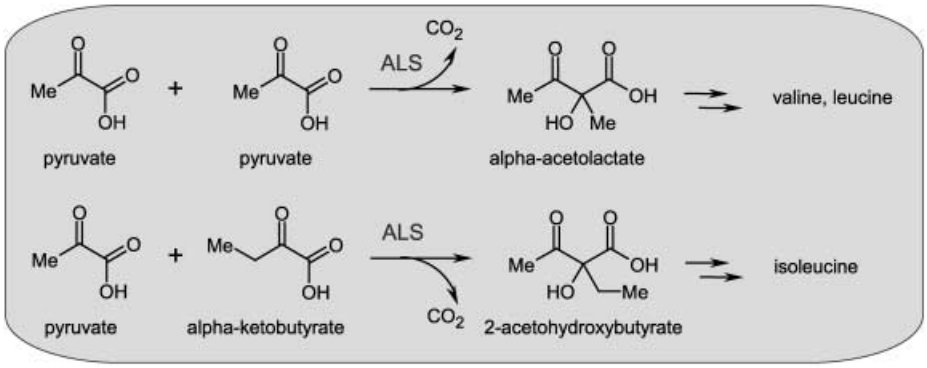


Figure 12. *Flufenacet (**84**) and flufenacet glutathione conjugate **85**.*

the reaction of flufenacet with glutathione results in the expulsion of the 5-trifluoromethyl-1,3,4-thiadiazole moiety.[112]



Scheme 19. *The action of acetolactate synthase, the target of many sulfonylureas.*

Sulfonylureas

The sulfonylureas represent a large and very successful class of selective herbicides[113] originally discovered by DuPont. They are the most active commercial herbicides to be developed, with a typical use rate of only grams per hectare. The first of these compounds to be launched was chlorsulfuron (**86**; Figure 13),[114] which is used for weed control in wheat and has a novel herbicide mode of action with acetolactate synthase (ALS)[115] as its target. ALS is a key enzyme in the biosynthesis of branched amino acids like leucine, isoleucine, or valine.[116] The enzyme catalyzes the condensation of two pyruvate molecules into α-acetolactate, as well as the condensation of pyruvate and α-ketobutyrate to form 2-acetohydroxybutyrate, with cleavage of carbon dioxide. In amino acid biosynthesis, α-acetolactate is further transformed into valine and leucine, whereas 2-acetohydroxybutyrate is a precursor of isoleucine (Scheme 19). Sulfonylureas are generally extremely potent inhibitors of this enzyme[117] regardless of the plant source, so different sensitivities at the target site hardly play a role in the selectivity of these highly efficacious herbicides. Approximately 62% of commercialized sulfonylureas are halogen free. Nearly a quarter of the sulfonylureas launched so far contain fluorine and only 14% have other halogens like chlorine or iodine in their composition. Exchange of the *ortho*-chlorophenyl group in the cereal-selective compound chlorsulfuron (**86**) with *ortho*-trifluoropropylphenyl (**87**; Scheme 20) leads to a selectivity shift and such changes facilitate the filing of patent applications. For sulfonylureas, crop selectivity is typically the result of selective metabolism of the active ingredient by the crop. The resulting maize-selective prosulfuron (**87**; Syngenta),[118] for example, is metabolized in maize by an additional hydroxylation at the methyl group of the triazine moiety.

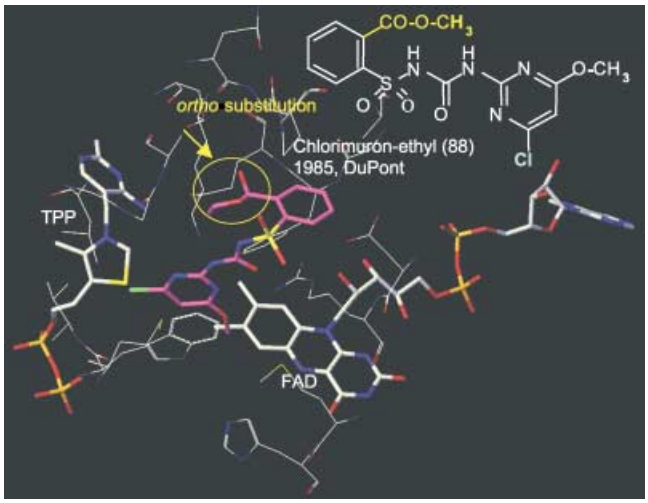
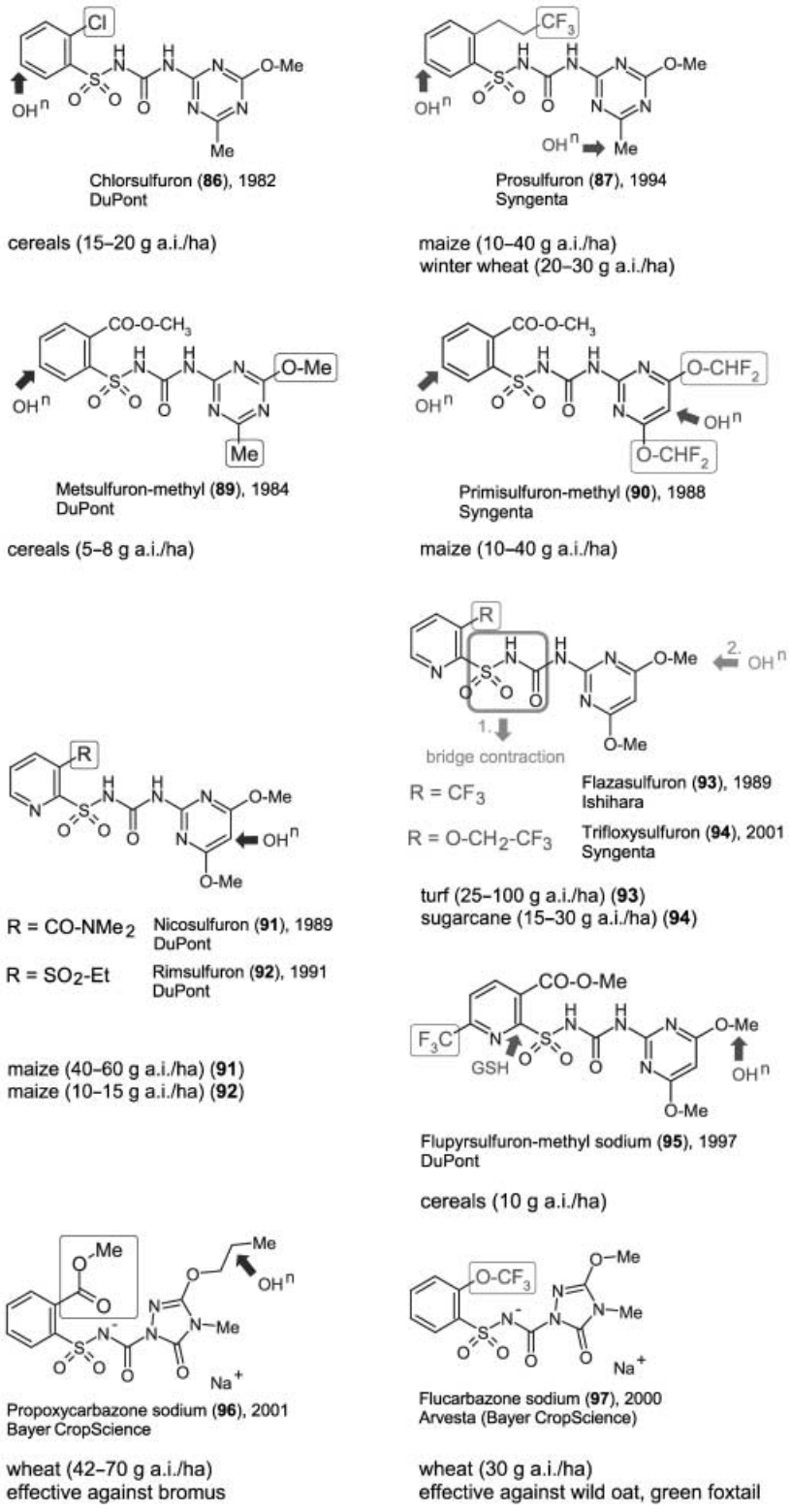


Figure 13. *Binding niche of yeast ALS; complex cocrystallized with chlorimuron-ethyl (**88**); data taken from S. S. Pang, L. W. Guddat, R. G. Duggleby,* J. Biol. Chem. ***2003****, 278, 7639–7644. TPP, thiamine pyrophosphate; FAD, flavin adenine dinucleotide.*

Recently, Pang and co-workers[119] described a 2.8 Å resolution crystal structure of yeast ALS as a complex with the sulfonylurea herbicide chlorimuron-ethyl (**88**; DuPont; Figure 13). From this structure it is evident that phenylsulfonylurea inhibitors with substituents in the *meta* or *para* position of the aromatic ring cannot be accomodated in the binding site of the enzyme and consequently show low or no herbicidal activity—structural variation of the herbicides is restricted to the *ortho* position.

Primisulfuron-methyl (**90**)[120] is a selective herbicide for the control of grasses in maize. Comparison with its unfluorinated triazine counterpart methsulfuron-methyl (**89**; Scheme 20)[121] indicates that crop safety for maize is achieved by the replacement of the triazine methoxy and methyl substituents with two difluoromethoxy groups. It has been shown that primisulfuron-methyl (**90**) is deactivated in maize by hydroxylation of the phenyl and pyrimidyl moieties followed by hydrolysis or conjugation. Comparison of nicosulfuron (**91**)[122] and rimsulfuron (**92**)[123] (which contain a 3-($CONMe_2$)-pyrid-2-yl and a 3-(SO_2-Et)-pyrid-2-yl moiety, respectively) with flazasulfuron (**93**)[124] shows that the 3-CF_3-pyrid-2-yl moiety present in **93** has a marked impact on the metabolism of this analogue (Scheme 20). 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 pyrimidyl methoxy substituent. In contrast to nicosulfuron (**91**) or rimsulfuron (**92**), flurpyrsulfuron-methyl sodium (**95**; DuPont) contains a 3-($COOCH_3$)-6-CF_3-pyridyl moiety, which influences the metabolic pathway. Besides glutathione conjugate formation, *O*-demethylation is predominant in the detoxification of flurpyrsulfuron-methyl sodium (**95**) in cereals.

The novel compound propoxycarbazone sodium (**96**; Attribut, Bayer CropScience)[125] offers the farmer an opportunity to exert effective, focused control over brome grasses, blackgrass,



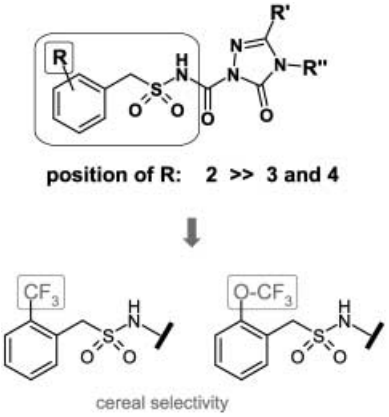
Scheme 20. *Influence of fluorine-containing substituents on selectivity and metabolism.*

and bentgrass. During optimization of the sulfonyl component it was found that the sulfonylaryl moiety is more active than the corresponding sulfonylmethylaryl moiety (Scheme 21). Particularly good activity and cereal selectivity were identified for substitution of the sulfonylaryl moiety with CF_3 and CF_3O. Exchange of the *ortho*-$COOCH_3$ substituent for an *ortho*-CF_3O residue in the sulfonylaryl moiety led to flucarbazone sodium (**97**),[126] a herbicide with excellent activity against grass weeds and several important broadleaf weeds when applied post-emergence to wheat. In field experiments, this product has demonstrated good, consistent activity against wild oat and green foxtail. At the suggested use rate of 30 g a.i./ha, both weeds were selectively controlled in wheat.

The various examples described above demonstrate that the introduction of fluorine has had a dramatic effect on the metabolism of the active ingredients through reaction at a location remote from the fluorinated groups themselves. However, such effects cannot often be predicted as part of the initial design of a molecule.

6. Summary and Outlook

The significant expansion in the use of fluorinated commercial agrochemicals is reflected by the presence of fluorine in 54% of herbicides/safeners, 27% of insecticides/acaricides, and 19% of fungicides on the market. In the search for an optimal product in modern crop protection in terms of efficacy, environmental safety, user friendliness, and economic viability (Figure 14), the substitution of active ingredients with fluorine is an important tool. However, the introduction of fluorine into a molecule can lead to an increase or a decrease in efficacy depending on the mode of action, physicochemical properties, or target interaction of the compound. The metabolism of the compound is influenced by the substitution pattern and by the soil stability and/or water solubility of the molecule. In general, the complex SARs within active ingredients make it difficult to predict sites



Scheme 21. *Optimization of the sulfonylmethylaryl moiety in sulfonylureas.*

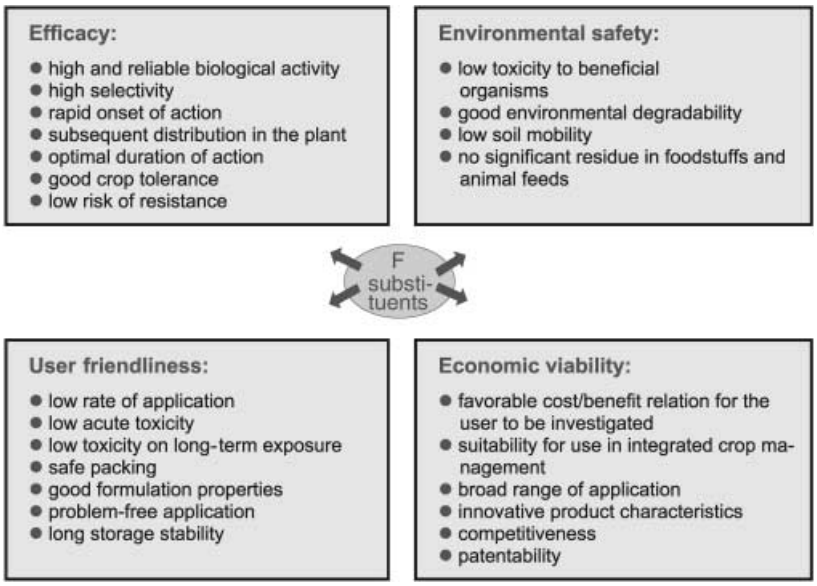


Figure 14. *The search for the optimal product in modern crop protection through the use of fluorine substituents.*

where fluorine or hydrogen substitution will increase biological activity. An indication shift can be observed upon introduction of fluorine into various biologically active molecules. The technical availability of molecules containing fluorine has been improved by an increase in access to new intermediates also on the market for pharmaceuticals. In future, the influence of fluorine on the action of biologically active molecules in relation to the desired improvement of lead structures has to be investigated by modern technologies.

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Keywords: crop protection · fluorine · fungicides · herbicides · insecticides · structure–activity relationships

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