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Changes in the Activity and Selectivity of Herbicides by Selective Fluorine Substitution, Taking Bentranil and Classic® Analogues as Examples

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Abstract: The introduction of fluorine atoms into 2-phenyl-4H-3,1-benzoxazin-4-one (bentranil) led to sweeping changes in its herbicidal properties in some cases, and 5-fluoro-2-phenyl-4H-3,1-benzoxazin-4-one ('fluorobentranil') was found to be the most active compound. It can be prepared from 2-amino-6-fluoro-benzoic acid or by direct halogen exchange of 5-chloro-2-phenyl-4H-3,1-benzoxazin-4-one. The latter reaction was investigated on a pilot scale, including a high-temperature (350 °C) potassium fluoride halogen exchange without solvent. When sulfolane was used as a solvent, a side reaction at 220 °C – partial decomposition to a diphenylether – could be prevented by addition of a small amount of a radical scavenger. Other intermediates with a pseudohalogen substitution were obtained by side-chain chlorination of suitable methylsulfanyl benzoic acid precursors and halogen exchange. 'Fluorobentranil' shows good broad-leaf activity and selectivity on rice, cereals and maize. In a second case study, the fluoro-substituted anthranilic acids mentioned above were also found to be appropriate for synthesizing herbicidal sulfonylurea (SU) compounds *via* Meerwein reaction of their aniline function. Methyl 2-[({[(4-chloro-6-methoxy-2-pyrimidinyl)-amino]carbonyl}amino)sulfonyl]-6-fluorobenzoate is an example of a SU that is compatible with maize, whereas the unsubstituted Classic® analogue is not selective.

Keywords: Fluoro-2-phenyl-4H-3,1-benzoxazin-4-ones · Fluoro sulfonylureas · Pseudohalogen benzoyl halides · SAR

1. Introduction

Fluorine substitution has, because of its influence on activity, selectivity, toxicity and environmental behaviour, become an outstanding tool in the design of modern agrochemicals. Of 45 new pesticide molecules presented at the annual Brighton Crop Protection Conference between 1998 and 2002, 15 contained one or more fluorine atoms, underlining the important contribution of fluorine.

BASF research has shown great interest substituting bentranil (Table 1; 2-phenyl-4H-3,1-benzoxazin-4-one) with fluorine in both the phenyl and the benzoxazinone moieties to investigate the influence of fluorine on the relationship between structure and activity. Bentranil, an early experimental BASF herbicide synthesized from anthranilic acid and benzoyl chloride, exhibits excellent selectivity in graminaceous crops, potatoes and to a lesser extent soybeans, has never been commercialised, because of the rather high dosage necessary to combat broadleaf weeds. While conventional σ ± substituents like methyl or nitro reduce herbicidal activity, a small increase is observed when the phenyl side chain is substituted by halide in the *m*-position. On the other hand, *o*- and *p*-derivatives are definitely inferior to the standard (Table 1). With halide as an indicator for the activating positions of the molecule – which are also potential positions for metabolic degradation – we were encouraged to investigate *m*-pseudohalides for the side chain and fluorine substitution in the heterocyclic moiety.

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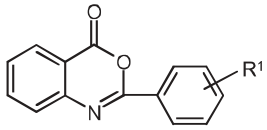
2. Material and Methods

2.1. *Synthesis of Halide Substituted Benzoxazinones*

Halide substitution in the 8- to 6-benzoxazinone positions was performed by oxidizing suitable *o*-toluidines to their anthranilic acids or by reacting substituted anilines with chloral/hydroxylamine to make isatoic acid intermediates (Scheme 1.1). To occupy the 5-position, 2,6-dichlorobenzonitrile was chosen as the starting material (Scheme 1.2). Halogen exchange with potassium fluoride gave 2,6-difluoro-benzonitrile, which was converted with ammonia under pressure at 100 °C to give 2-amino-6-fluoro-benzonitrile, followed by saponification of the nitrile to the acid, with 83% overall yield [1][2]. The next step, synthesis of the heterocycle (Scheme 1.3) was optimized in the following way: Anthranilic acids were reacted with benzoyl chloride in a two-phase sys-

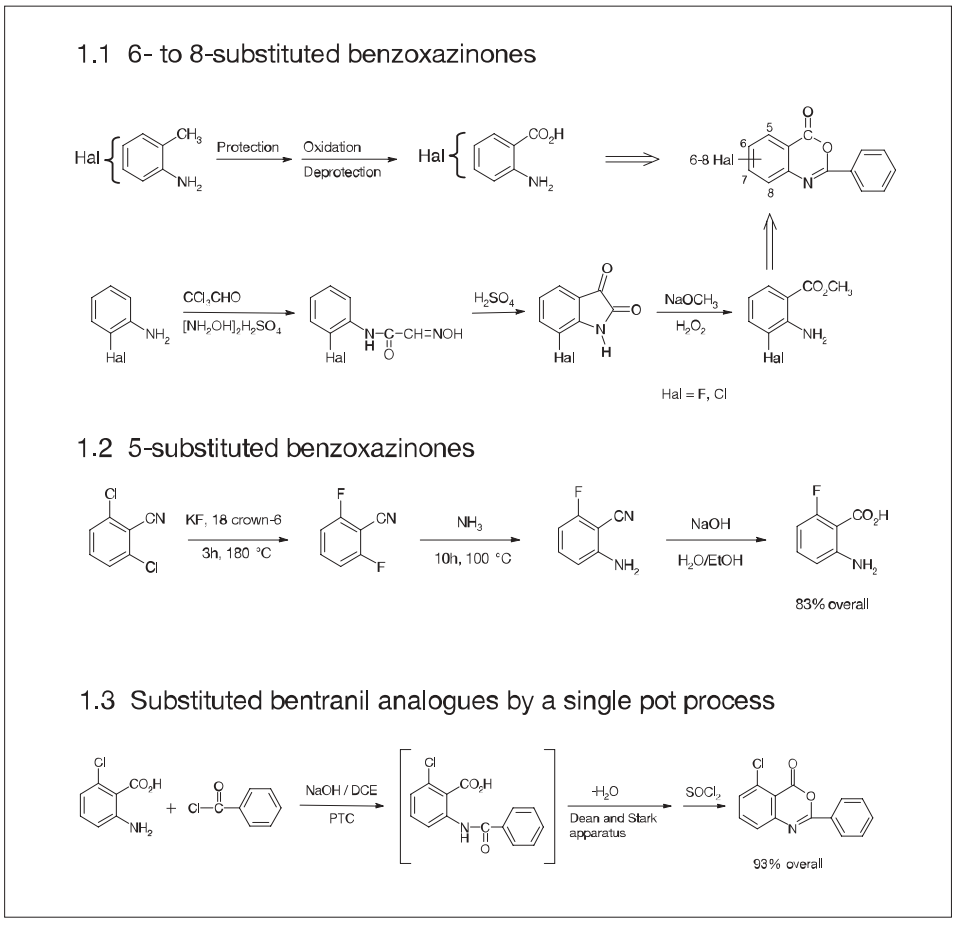
Table 1. SAR in the phenyl side chain (R^1)



bentranil R^1=H

Test plants and activity
(0.5kg/ha: oil-SC)

R^2	$\bar{X}$-activity [%]	*Sinapis alba*	*Chenopodium album*
H	97,5	95	100
2-Cl	35	0	70
3-Cl	100	100	100
4-Cl	10	0	20
3-F	100	100	100
4-F	55	20	90
3-CH_3	37,5	0	75
3-OCH_3	17,5	0	35
3-NO_2	27,5	-	55
3-CF_3	89	89	89



Scheme 1. Access for substituted benzoxazinones *via* suitable anthranilic acids and a single pot process

tem with aqueous sodium hydroxide in dichloroethane under phase-transfer catalysis and cyclized in a single-pot procedure in 93% overall yield. The intermediate benzamide was not isolated and water was azeotropically removed before cyclization.

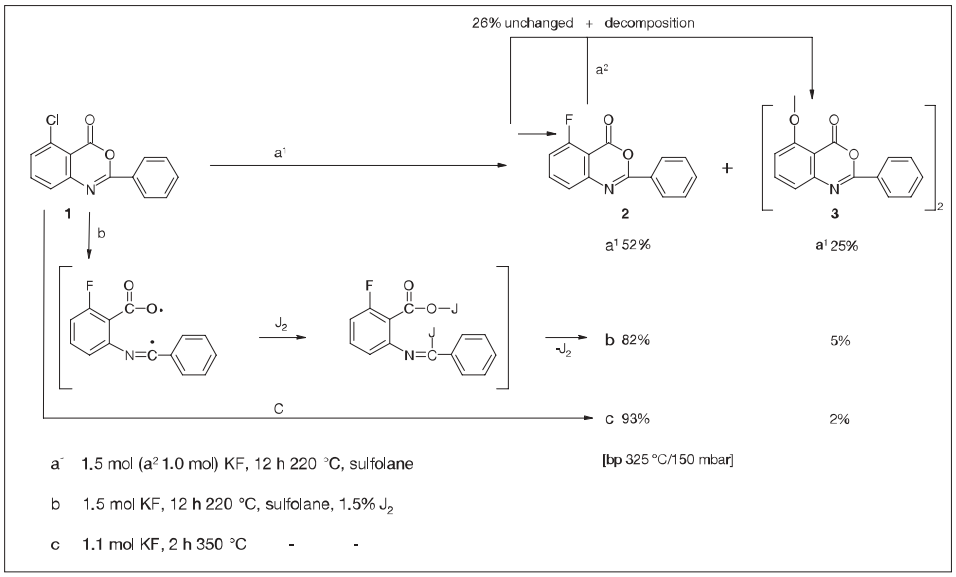
2.2. *Development of a Technical Process for 5-Fluoro-2-phenyl-4H-3,1-benzoxazin-4-one*

In comparison to a halogen exchange of 2,6-dichlorobenzonitrile as a starting material for the desired anthranilic acid, postponing the expensive halogen exchange reaction until the last step (Scheme 2) should be advantageous. Unfortunately conventional halogen exchange of **1** to 5-fluoro-2-phenyl-4H-3,1-benzoxazin-4-one (**2**) with potassium fluoride at 220 °C in sulfolane was accompanied by a strong side reaction resulting in the formation of a heterocyclic (ether) dimer **3** (25%), so that the yield of **2** was only 52% (reaction a^1). This became more comprehensible when pure **2,** after 12 h treatment with an equimolar amount of potassium fluoride in sulfolane at 220 °C (reaction a^2), contained only 26% of unchanged starting material, the remainder being decomposition products with **3** predominating. Nucleophilic side reactions of potassium fluoride with acyl groups are also known from the literature. For example, when Odinokov and coworkers [3] reacted 3,6-di-chlorophthalic anhydride **4** with potassium fluoride at 190–200 °C they obtained the expected difluoro compound **5**, but at 240 °C partial decarboxylation gave rise to a dimeric lactone **6** (Scheme 3). In our search for decomposition inhibitors it was found that addition of 1.5 mol% iodine (Scheme 2, reaction b) reduced the side reaction from 25% to 5% and increased the yield of **2** to 82% [4]. Our suggested mechanism is only tentative. Molecular iodine acts either as a Lewis acid, reducing the basicity of soluble potassium fluoride, or as a radical scavenger. In the literature, acyl hypoiodides have also been formulated by iodination of acetic acid in the presence of oxidative reagents [5].

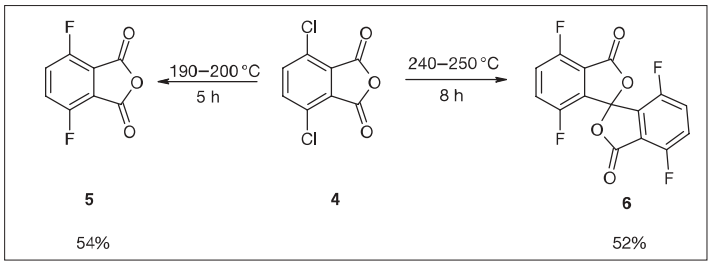
Success can sometimes be achieved by completely omitting the solvent. Even at 300 °C, there was no reaction, but at 350 °C a 93% conversion to the 5-fluoro-benzoxazinone **2** with only 2% concomitant side reaction was observed (Scheme 2, reaction c) [4]. The reduction of basicity and nucleophilicity in our solid-liquid reaction melt compared with the sulfolane procedure may be the reason for the almost quantitative halogen exchange. The desired product was distilled continuously out of the reaction melt and therefore separated from the diphenyl ether **3** and other side products. The reaction was further optimized under technical conditions in a Hastelloy C4 vessel, where a reaction time of 2 h and easy work-up conditions were achieved.

2.3. *Synthesis of Pseudohalide Substituted Benzoyl Halides*

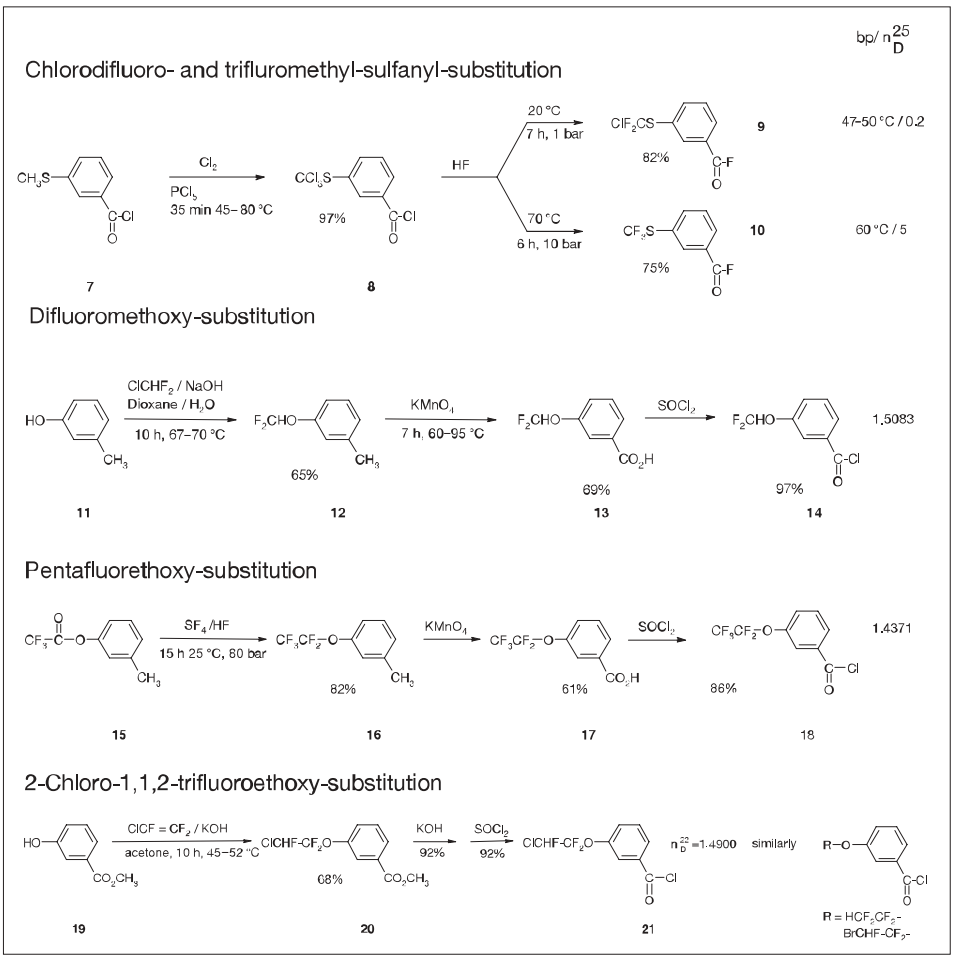
To produce the side-chain-fluorinated benzoyl halides, the precursors for the right half of our benzoxazinone heterocycle, we started from compounds such as 3-(methylsulfanyl)benzoyl chloride (**7**) (Scheme 4). Chlorination under mild conditions with phosphorus pentachloride as a catalyst and a temperature of 45–80 °C resulted in a high yield of the trichloromethylsulfanyl compound **8** [6]. Under similar conditions to



Scheme 2. Halogen exchange reactions for 5-fluoro-2-phenyl-4H-3,1-benzoxazin-4-one



Scheme 3. Potassium fluoride induced decomposition in the literature



Scheme 4. Side-chain fluorinated benzoyl halides

those described for fluorinated anisoles, **8** was converted with hydrogen fluoride at low temperature and pressure to 3{[chloro-difluoro)- methyl] sulfanyl}benzoyl fluoride (**9**), while reaction at 70 °C and 10 bar pressure gave the trifluoro compound **10** [7][8]. Both products were obtained in good yields. A lower degree of fluorination was achieved by adding chlorodifluoro-methane to *m*-cresol **11** in dioxane/water at 67–70 °C in 65% yield, oxidizing to the acid **13** and reacting further to give the acid chloride **14** [9]. Higher fluorinated derivatives were obtained following a suggestion from Yagupolskii, the well-known Russian pioneer in fluorine chemistry: reaction of 3-methyl-phenyl trifluoroacetate **15** with sulphur tetrafluoride in liquid hydrogen fluoride at 25 °C and 80 bar pressure [9][10]. The yield was 82%. We did not optimize oxidation to the acid **17,** for which the yield was 61% [9]. This was followed by thionylchloride reaction to the 3-(1,1,2,2,2-penta-fluoroethoxy)benzoyl chloride **18** [9]. Mixed chloro/fluoroethoxybenzoyl chlorides were prepared in analogy to D.C. England's early work in the 1960s by addition of 1-chloro-1,2,2-trifluoro-ethene to methyl 3-hydroxybenzoate (**19**) in 68% yield, rapid hydrolysis and further reaction to the 3-(2-chloro-1,1,2-trifluoroethoxy) benzoyl chloride **21** [9][11].

2.4. *Synthesis of Fluoro Substituted Sulfonylureas*

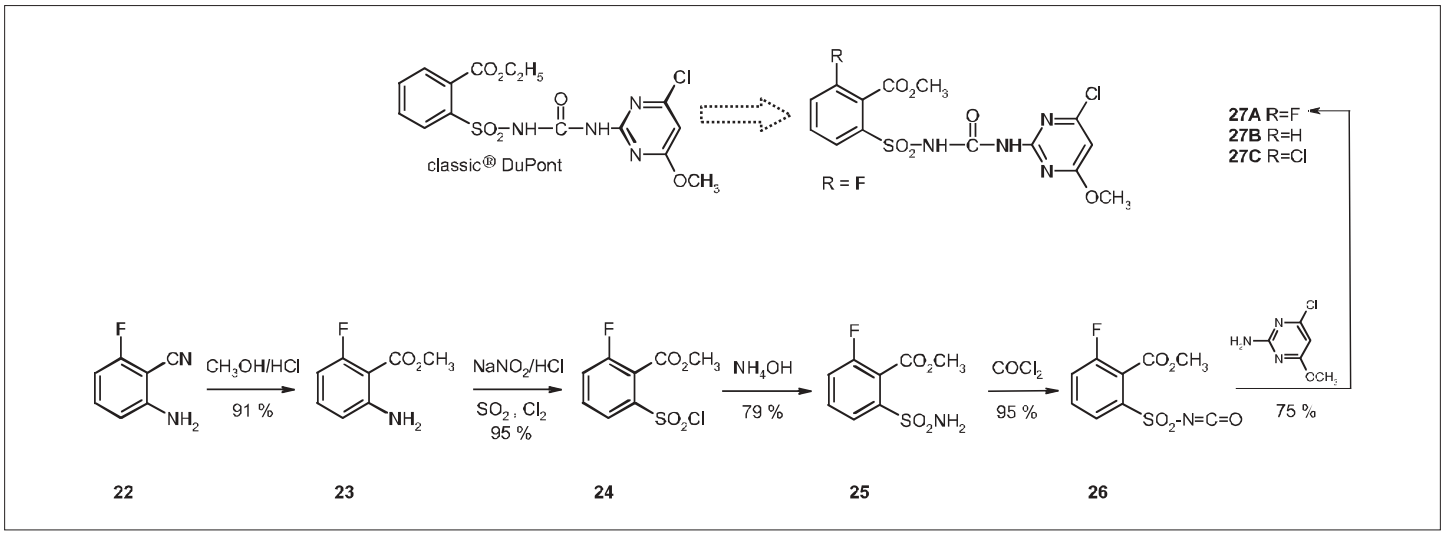
The ready availability of a number of new fluorine intermediates and improved access to known ones prompted research on other leads. In this respect our fluoroanthranilic esters seemed appropriate building blocks for investigating sulfonylureas (SUs), most of which are based on benzenesulfonamides with an *o*-ester substituent. Classic® (chlorimuron) from DuPont is an early example of an SU with selectivity in soybeans and low application rates of 35–53 g/ha for the control of broadleaf weeds (Scheme 5) [12].

Starting material was the above-mentioned 2-amino-6-fluoro-benzonitrile (**22**). Both its Pinner reaction to the ester **23** and the Meerwein reaction were performed in more than 90% yield, giving very smooth access to substituted benzenesulfonyl chlorides **24**. The next steps were reaction with aqueous ammonia and phosgenation in good yield to the isocyanate **26**, which readily allowed 2-amino-4-chloro-6-methoxy-pyrimidine to be added to the SU **27A** with 3-fluoro substitution in the benzene sulfonamide moiety [13]. The yield was 75%. Similarly the 3-chloro compound **27C** was prepared.

2.5. *Biological Tests*

2.5.1. *Greenhouse Experiments*

All the data were taken from screening-type trials in the greenhouse. For post-



Scheme 5. Sulfonyl ureas derived from 3-fluoro-2-methoxy-carbonyl-benzenesulfonamide

emergence tests, plants were cultivated in plastic pots of 8.6 cm diameter containing loamy sand with about 1.2% humus as the substrate. The test plants were sown, grown in the test pots to a height of 4–12 cm and then treated with the test compound in a spray chamber at a rate of 0.25–0.5 kg/ha a.i. (active ingredient) for the benzoxazinones and 62.5 g/ha a.i. for the sulfonylureas, formulated as emulsion concentrates. The number of replicates was one and, for comparison, four untreated control pots were included in each test. After the application, the test plants were kept for 18–20 days at 18–27 °C, during which period the plants were maintained and their reaction to the individual treatments was assessed and recorded. Injury to the plants was assessed on a scale from 0 to 100 in comparison to the untreated controls, with 0 denoting no damage and 100 denoting complete destruction of at least the visible plant parts.

2.5.2. *Test Species*

The following plant species were used: Broadleaf weeds: velvet leaf (*Abuthilon theophrasti*), redroot pigweed (*Amaranthus retroflexus*), hairy beggarticks (*Bidens pilosa*), common lambs-quarters (*Chenopodium album*), bengal commelina (*Commelina benghalensis*), florida beggar weed (*Desmodium tortuosum*), wild poinsettia (*Euphorbia heterophylla*), cleavers (*Galium aparine*), annual mercury (*Mercurialis annua*), chamomile (*Matricaria spp.*), tall morning glory (*Pharbitis purpurea*), ladysthumb (*Polygonum persicaria*), hemp sesbania (*Sesbania exaltata*), wild mustard (*Sinapis arvensis*), black nightshade (*Solanum nigrum*), and maize (*Zea mays*).

3. Results and Discussion

3.1. *Structure–Activity Relationship (SAR)*

3.1.1. *Benzoxazinones*

With these benzoxazinones available, standard screening trials were conducted in the greenhouse with post-emergence treatment of different crops containing broadleaf weed species at 0.5 kg/ha ai, formulated as a suspension concentrate. While chlorine (Table 2) induces a loss of activity – except in the 5-position, where it is equivalent to the standard – a continuous increase in activity was observed as the hydrogens were replaced stepwise by fluorine on passing from the 7- to the 5-position. The 8-fluoro derivative was weaker than the parent compound, but surprisingly the 5-fluoro derivative proved to be about three times as active as the standard. Table 3 shows the average activity on seven plant species on a scale of 0 to 100 and the lipophilicity (log P) measured by standard HPLC procedure. While dichloro **29** for both R^1 and R^2 or a combination of nitro and chlorodifluoromethoxy **33** reaches only medium activity with less than 50%, high activity is observed for chloro and pseudohalide side-chain substituents connected to fluorine- or chlorine-substituted anthranilic acid. When phytotoxicity is correlated with lipophilicity (Fig. 1), three different clusters can be identified: 5-fluoro-3,1-benzoxazine-4-ones and their corresponding 5-chloro derivatives, each with fluorine side chains, as compared to the unsubstituted bentranil **28**. The 5-fluoro-3,1-benzoxazin-4-ones show only a very small range of lipophilicity with 3.7 as the optimum, while the chloro derivatives show a better parabolic relation with log P = 4.3 as the optimum.

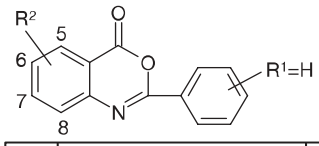
What can be clearly seen is the effect of several fluorine atoms adding to the overall lipophilicity compared with the unsubstituted standard **28** with a log P = 3.3. Introducing only one fluorine atom into the anthranilic acid moiety of the standard results in log P = 3.2 (compound **2**). As expected, the lipophilicity difference in both cases is small and shows once again the similarity of hydrogen and fluorine in a bioactive molecule as far as size and lipophilicity are concerned. But fluorine, being much more electronegative, apparently binds better to the enzyme, resulting in higher activity. In fact, this compound turned out to be the most active derivative. At 250 g/ha, 5-fluoro-2-phenyl-4H-3,1-benzoxazin-4-one controlled numerous weed species and possessed excellent selectivity in several crops. Results were confirmed by field trials at rates of 0.5 kg/ha (Table 4).

3.1.2. *Sulfonylureas*

The herbicidal activity of the Classic® analogues was compared on six broadleaf weeds in the greenhouse at an application rate of 62.5 g/ha (Fig. 2). Derivative **27B** achieved the highest activity with a sum of 585, but was followed very closely by the fluoro and chloro derivatives **27A** and **27C** with sums of 560 and 561 respectively. The difference in selectivity is critical.

While the unsubstituted SU has no selectivity at all on maize and the chloro compound still produces 50% damage on maize, the fluoro derivative is much safer and shows only 10% damage three weeks after treatment – damage that later assessments show to have grown out.

Table 2. SAR in the anthranilic acid moiety (R^2)

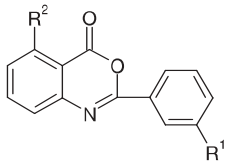


Test plants and activity (0. kg/ha: WP*)

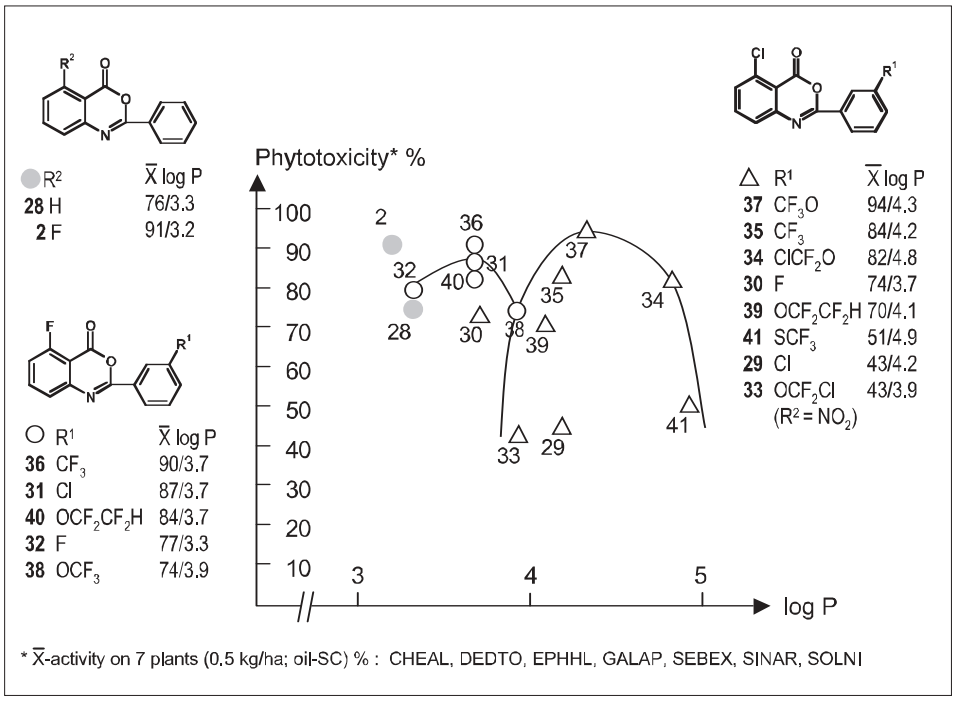
R^2	$\bar{X}$-activity [%]	*Sinapis alba*	*Chenopodium album*	*Matricaria spp.*	*Mercurialis annua*
H	28.3	53	60	0	0
5-Cl	30	13	38	33	36
6-Cl	1.5	3	0	3	0
7-Cl	0	0	0	0	0
8-Cl	0	0	0	0	0
5-F	86.8	54	95	99	99
6-F	59	74	48	27	87
7-F	36.3	69	50	13	13
8-F	3.3	3	7	0	3

* Wettable Powder

Table 3. SAR in the m-phenyl side chain (R^1) + anthranilic acid moiety (R^2)



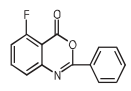
No.	log P	R^2	R^1	$\bar{X}$-activity on 7 plants (0.5kg/ha; oil-SC, [%]	$\bar{X}$
28	3.3	H	H		76
29	4.2	Cl	Cl		43
30	3.7	Cl	F		74
31	3.7	F	Cl		87
32	3.3	F	F		77
33	3.9	NO_2	OCF_2Cl		43
34	4.8	Cl	OCF_2Cl		82
35	4.2	Cl	CF_3		84
36	3.7	F	CF_3		90
37	4.3	Cl	OCF_3		94
38	3.9	F	OCF_3		74
39	4.1	Cl	OCF_2CF_2H		70
40	3.7	F	OCF_2CF_2H		84
41	4.9	Cl	SCF_3		51
2	3.2	F	H		91



* $\bar{X}$-activity on 7 plants (0.5 kg/ha; oil-SC) % : CHEAL, DEDTO, EPHHL, GALAP, SEBEX, SINAR, SOLNI

Fig. 1. SAR in the m-phenyl side-chain + anthranilic acid moiety – dependence of phytotoxicity on log P

Table 4. Weed spectrum of 5-fluoro-2-phenyl-4H-3, 1-benzoazin-4-one



250 g/l – SC/water-oil

Crops:	Weed species:		
Barley	*Alisma spp.*	*Cyperus esculentus**	*Papaver rhoeas*
Oats	*Ammania coccinea*	*Cyperus iria*	*Polygonum aviculare*
Wheat	*Anthemis arvensis*	*Desmodium tortuosum*	*Polygonum convolvulus*
Corn	*Atriplex patula*	*Galeopsis tetrahit*	*Raphanus raphanistrum*
Rice	*Bidens pilosa*	*Galinsoga parviflora*	*Sagittaria sagittifolia*
Sorghum	*Capsella bursa pastoris*	*Galium aparine*	*Sesbania exaltata*
Irish Potatoes	*Centaurea cyanus*	*Ludwigia spp.*	*Sinapis spp.*
Peanuts	*Chenopodium spp.*	*Matricaria spp.*	*Thlaspi arvense*
	Chrysanthemum spp.	*Mercurialis annua*	*Vicia spp.*
	Cirsium arvense	*Myosotis arvensis*	*Xanthium pensylvanicum*
	Cyperus difformis	*Nicandra physaloides*	

Confirmed by field trials at rates of ± 0.5 kg/ha a.i. *higher rates

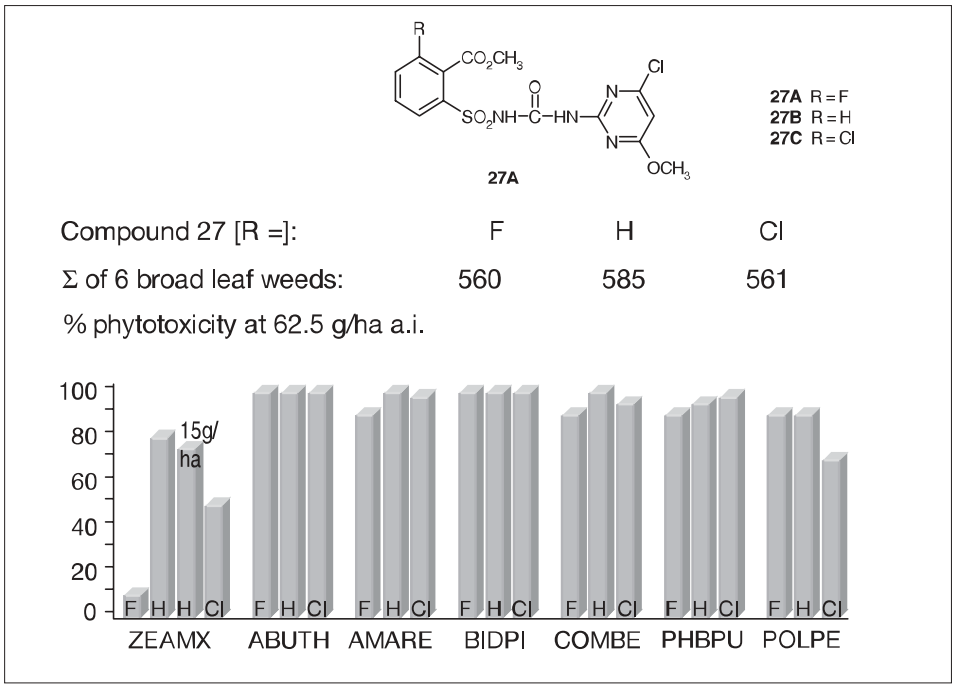


Fig. 2. Influence of halide substitution in the benzenesulfonamide moiety

4. Conclusion

The first case study in bentranil chemistry gave an example of where substitution of hydrogen by fluorine at a specific position in the heterocycle led to an impressive rise in activity. The second SU case study showed what surprising selectivity can be obtained by substituting fluorine for hydrogen in the right position.

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