Invited Trends Article

Peroxidizing Herbicides (II): Structure-Activity Relationship and Molecular Design

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Diphenyl Ethers, Cyclic Imides, Structure and Activity, Molecular Design, Conversion of Isoimides

Introduction

The *p*-nitrodiphenyl ethers (DPEs) and cyclic imides (CyIs), here called peroxidizing herbicides of the first generation (1965–1980), induce inhibition of chlorophyll biosynthesis and photooxidative destruction of plant membranes affecting photosynthetic pigment contents. The detailed mechanism of action of the peroxidizing herbicides has been outlined in the first part of this review (Böger and Wakabayashi, 1995). The immediate physiological response of the plant against these herbicides is a halt of chlorophyll biosynthesis in chloroplasts by specific inhibition of protoporphyrinogen-IX oxidase (protox). This inhibition is accompanied by an abnormal accumulation of protoporphyrin-IX (proto-IX or a derivative thereof), which acts as a photosensitizer in the light and induces radical formation with subsequent destruction of cellular constituents. The old light-dependent herbicidal-action theory of DPEs and CyI compounds (Matsunaka, 1969; Matsunaka, 1976; Suzuki *et al.*, 1975; Wakabayashi *et al.*, 1979; Fedtke, 1982) can be now discussed on the basis of this principle.

The substantial steps made forward in recent years to elucidate the mechanism of action gave a strong impetus to molecular design of the second generation (since 1980) of peroxidizing herbicides. At least 20 different herbicide candidates including CyIs, pyrazoles, triazoles, triazolidines, thiadiazolidines and oxazolidines with an N-(2-fluoro-4-chloro-5-substituted)phenyl moiety, 2-chloro-4-trifluoromethylphenyl 3′- substituted-4′-nitrophenyl ethers, and certain pyridine derivatives are currently in development and more may be investigated (Fig. 1; Wakabayashi and Böger, 1993, 1994). The basic structures of peroxidizing herbicides including those of 1st and 2nd generation can now classified into five larger groups: (1) diphenyl ethers, (2) cyclic imides, (3) N-aryldiazoles, (4) N-heterocyclic five-membered compounds without N-aryl linkage, and group (5) including compounds with a pyridine-carboxamide or a carbamate moiety (Fig. 2). Oxyfluorfen and SUAM-16476 of group 1 are representatives of the most active DPE peroxidizers. Within the five groups, the CyI class (group 2) is most flourishing in designing new peroxidizing herbicides, starting from modification of the old parent compound, chlorophthalim, as outlined by Fig. 3. To design CyI-type peroxidizers, the N-(2-fluoro-4-halogen (C1 or Br)-5-substituted) aryl moiety is essential to produce highly active compounds (Wakabayashi *et al.*, 1979; Wakabayashi, 1988). Herbicides of group 3 and 4 of Fig. 2 are the immediate family of CyI peroxidizers. It should be noted that in the pyrazole series of group 3 a 2,4,6-substituted aryl moiety proved to be effective. More recent N-heterocyclic five-membered peroxidizers (group 4) without an N-aryl linkage to the heterocycle should be emphasized (Miura *et al.*, 1993; Miura *et al.*, 1994; Hamper *et al.*, 1995), indicating that an N-aryl linkage, although dominant in peroxidizers, is not mandatory. The active compounds of this series include the C-(2-fluoro-4-halogen-5-substituted) aryl moiety, which markedly contrib-

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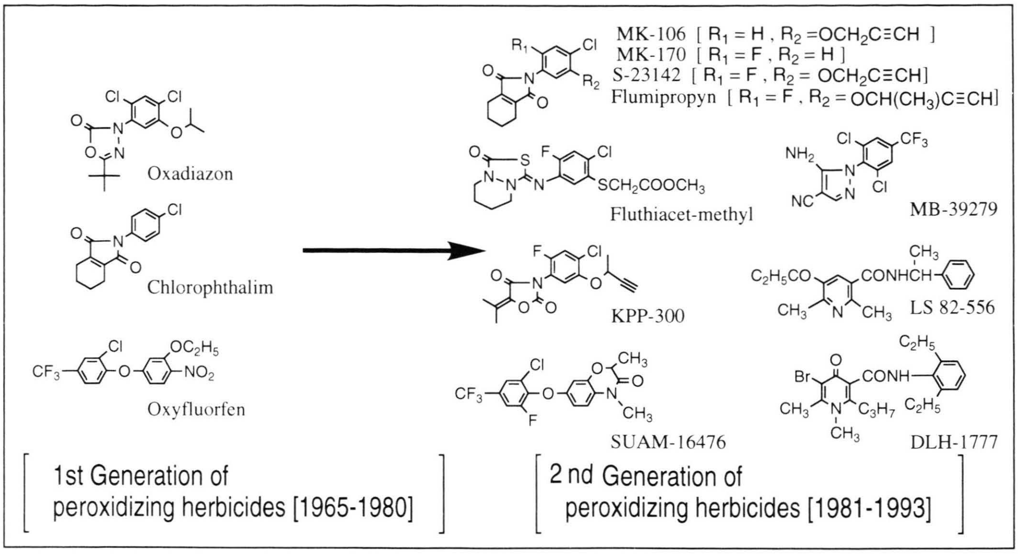


Fig. 1. Development of peroxidizing herbicides: Two generations since 1965.

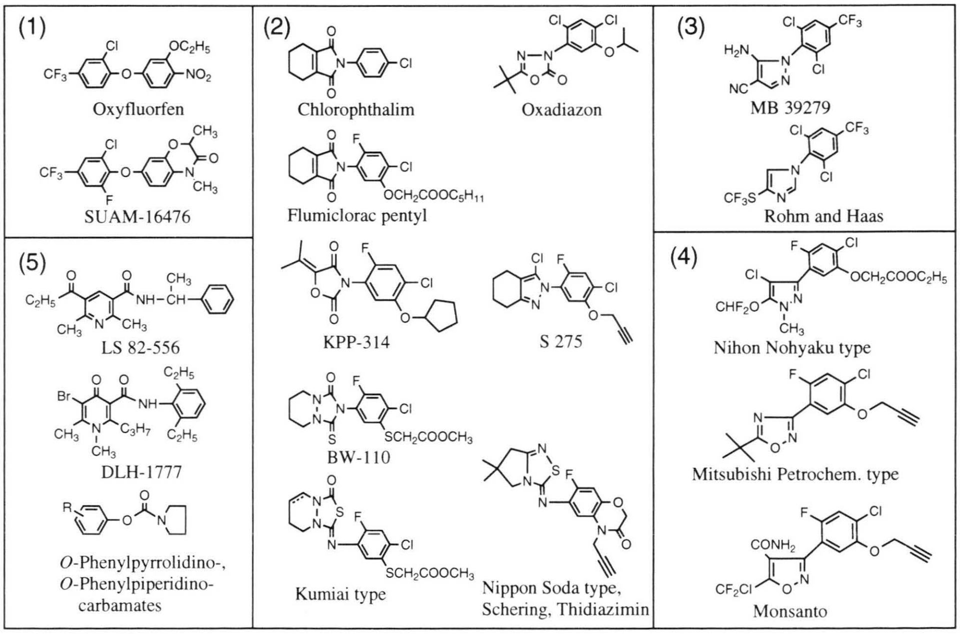


Fig. 2. Peroxidizing herbicides: The basic structures can be arranged in five groups.

utes to design peroxidizers with a lower use rate than found with the original CyI class of peroxidizers of group 2. Many of the CyI compounds with N-aryl linkage, however, are unstable in the environment (Sato *et al.*, 1991; Hoshi *et al.*, 1993; Sato *et al.*, 1994a; Iida *et al.*, 1995). Compounds belonging to group 5 have also been confirmed as peroxidizers, although their activity is not so strong compared with the other four groups (Wakabayashi and Böger, 1993).

Molecular design of peroxidizing herbicides has been integrated into other scientific disciplines,

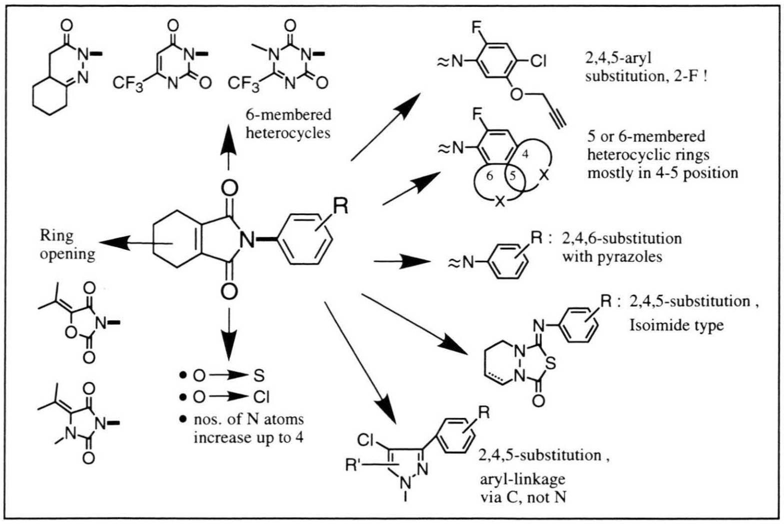


Fig. 3. The lead structure, an N-aryl-tetrahydrophthalimide can be modified as indicated by the formulas assigned to the arrows.

e.g. biochemistry, plant physiology, weed biology, to understand and optimize the phytotoxic properties. This review has the following three objectives concerning molecular design, giving a bird's-eye view of development of the peroxidizing herbicides:

(1) To find out what structural modification can be made to the parent compound without losing its unique phytotoxic properties. This information should indicate an optimized feature of the molecule essential for its activity.

(2) To find out whether the parent peroxidizers are active *per se*, or whether their activity results from modification within,or in the vicinity of, the plant cells.

(3) To design new peroxidizing herbicides with similar or improved activity by making use of the results analyzed.

Consideration of the First Generation of Peroxidizing Herbicides

The DPEs and CyIs, exhibiting the socalled light-dependent herbicidal action and bleaching activity related to photooxidative destruction of thylakoid and cell membranes, are now verified as peroxidizing herbicides (Wakabayashi and Böger, 1993; Böger and Wakabayashi, 1995). Several key studies sorting new leads have been introduced and are discussed here.

1. SAR studies of DPE and CyI peroxidizers

Diphenyl ethers: Various analogues have been assayed to find a correlation between chemical structures, their peroxidizing activity and protox inhibition (Lambert *et al.*, 1983; Nandihalli *et al.*, 1992). Many 2-chloro-4-trifluoromethylphenyl 3′-substituted-4′-nitrophenyl ethers exhibit protox inhibition and light-induced peroxidation. 3′-Substituents, such as $COOCH_3$, OCH_3, OC_2H_5, NHC_2H_5 and $CONHCH_3$, enhance the peroxidizing activity. A free carboxyl group in 3-position will reduce activity, its esterification generally markedly increases activity. Activity will be generally enhanced by substituents with positive Hammett σ parameters at 2- or 4-position at the phenyl ring not bearing a nitro group. Neither protox inhibition nor initial phytotoxic activity is changed by substituting 4′-chloro for a 4′-nitro group. The phytotoxic activity is completely lost when the CF_3-group is moved from 4- to 5-position. Compounds with S, SO, SO_2 or an NH-linkage between the two phenyl rings are herbicidally inactive. The promising structures of peroxidizing herbicides are shown in Fig. 4 (left part).

Cyclic imides: It has already been considered that the peroxidizing activity of CyIs is extremely high amongst compounds whose structures conform to the following rule (see Fig. 4, right part; Wakabayashi *et al.*, 1979; Wakabayashi, 1988;

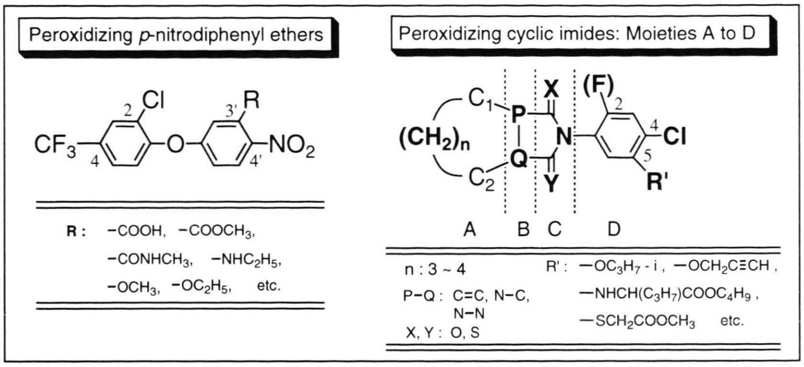


Fig. 4. Modification of active diphenyl ether and cyclic-imide type peroxidizers.

Wakabayashi and Böger, 1993): (1) C_1 and C_2 carbon atoms in moiety A should form an alkylene ring. A suitable lipophilicity of the alkylene group may play an important role to produce high activity. (2) Moieties B and C should form a planar arrangement. The double bond and bridgehead nitrogen atom(s) in the electron-donating moiety B may play a concerted role for the mechanism of action. (3) The 4-substituent on the benzene ring in moiety D should have a proper size and orientation (see chapter 2 on QSAR studies). A *p*-substitutent, like halogen (especially C1 or Br), lower alkyl, lower alkoxy or a benzyloxy group is essential for activity. Introduction of another halogen atom (especially F) at 2-position of the active 4-substituted aryl derivatives substantially enhances the peroxidizing activity. Introduction of an accessory substituent, such as alkoxy, alkenyloxy, alkinyloxy, amino acid, carboxymethyl-thio group and the like, as well as a 5-substituent at the active 4- or 2,4-arylsubstituted compounds increases activity. Certain 5-substituents (e.g. amino acid residues or a carboxymethylthio group may possibly undergo metabolic modification thereby contributing to selectivity (e.g. in fluthiacet methyl; Shimizu *et al.*, 1995 and personal commun.). The compounds of this line of molecular design may improve their uptake by plant cells or the affinity for the target enzyme protox (Kohno *et al.*, 1993). The 2-fluorophenyl group fused together with heterocyclic rings mostly in 4–5 position also produces quite good peroxidizing activity in recent molecular design (Wakabayashi and Böger, 1993; comp. Fig. 3).

2. QSAR studies on peroxidizing herbicides

For a large number of compounds, it has been established that their herbicidal efficiency in greenhouse tests and growth-inhibition activity against *Echinochloa* can be quantitatively correlated with high significance through the peroxidative phytotoxic parameters obtained from autotrophic *Scenedesmus* cells (Böger and Wakabayashi, 1995; Wakabayashi *et al.*, 1988; Watanabe *et al.*, 1992; Böger and Sandmann, 1994). Those are growth inhibition, decrease of chlorophylls and carotenoids, short-term accumulation of proto-IX and light-induced ethane formation, even the protox inhibition using corn etioplasts can be now combined with this network. A reliable quantitative correlation has been established with the six parameters mentioned. For example, QSARs of the peroxidizing compounds can be accomplished either with the *Echinochloa* root-growth inhibition test, by measuring light-induced ethane formation, or with decrease of chlorophyll content in sensitive green microalgae. The investigator may choose any one of the six parameters, whichever he can handle best in the laboratory.

The QSARs between structures and phytotoxic parameters obtained from 40 N-aryl-3,4,5,6-tetrahydrophthalimides have been analyzed using physico-chemical parameters and regression analysis (Ohta *et al.*, 1980; Wakabayashi, 1988; Sato *et al.*, 1992). The results shown in Table I indicate that the position-specific steric effect of aromatic substituents, as presented by the STERIMOL values of *para*-substituents, are highly important in determining the phytotoxic potency of cyclic imide

Table I. Quantitative structure-activity relationship of cyclic imide peroxidizers (N-aryl-3,4,5,6-tetrahydrophthalimides).

pI_{50} (*Echinochloa*)	$= 4.062$	-0.876σ	$+2.086Lp$	$-0.370Lp^2$	$-1.079B_5p$	(1)
	(± 0.197)	(± 0.383)	(± 0.336)	(± 0.098)	(± 0.221)	
				$[n = 40, r = 0.912, s = 0.345]$		
pI_{50} (*Scenedesmus*)	$= 5.595$	-0.944σ	$+2.652Lp$	$-0.471Lp^2$	$-1.380B_5p$	(2)
	(± 0.252)	(± 0.487)	(± 0.427)	(± 0.125)	(± 0.282)	
				$[n = 40, r = 0.912, s = 0.439]$		
pI_{50} (Chlorophyll)	$= 5.738$	-1.174σ	$+2.768Lp$	$-0.508Lp^2$	$-1.390B_5p$	(3)
	(± 0.264)	(± 0.513)	(± 0.450)	(± 0.131)	(± 0.296)	
				$[n = 40, r = 0.909, s = 0.462]$		
pI_{50} (Carotenoid)	$= 5.688$	-1.155σ	$+2.773Lp$	$-0.505Lp^2$	$-1.412B_5p$	(4)
	(± 0.258)	(± 0.502)	(± 0.441)	(± 0.128)	(± 0.291)	
				$[n = 40, r = 0.914, s = 0.452]$		
pI_{50} (Ethane)	$= 5.200$		$+0.772Lp$	$-0.041Lp^2$	$-0.304B_5p$	(5)
	(± 0.171)		(± 0.307)	(± 0.031)	(± 0.254)	
				$[n = 13, r = 0.985, s = 0.145]$		
pI_{50} (Protox)	$= 5.417$		$+2.172Lp$	$-0.195Lp^2$	$-0.947B_5p$	(6)
	(± 0.443)		(± 1.104)	(± 0.110)	(± 0.899)	
				$[n = 16, r = 0,900, s = 0.493]$		

pI_{50} values were determined by a root growth inhibition assay with *Echinochloa utilis* in a light/dark regimen (Eqn. (1)), growth inhibition of autotrophic *Scenedesmus acutus* (Eqn. (2)), decrease of chlorophyll and carotenoids in autotrophic cultures (Eqns (3), (4)), light-induced ethane formation by *Scenedesmus acutus* (Eqn. (5); the pI_{50} value really is the "activity value" as explained in Böger and Wakabayashi, 1995). Eqn. (6) represents the structure-activity relationship of STERIMOL parameters with the inhibition of isolated protoporphyrinogen oxidase from corn (*Zea mays*). $\sigma = \Sigma$ (Hammett σ constants of substituents). Lp is the STERIMOL parameter for the length along the bond axis connecting C (*para*) and the atom of the *para*-substituents. B_5p is the largest one among the STERIMOL width parameters of *para*-substituents. n is the number of experimental data, s the standard deviation, and r the correlation coefficient. Figures in parentheses are the 95% confidence intervals.

peroxidizers. In Eqns (1) to (6), the phyto-toxic activities are satisfactorily delineated by taking into account the combined electronic effect expressed as $\Sigma\sigma$ as well as the steric influence of *para*-substituents, although the σ term is not significant in Eqns (5) and (6) due to insufficient number (n) of data available on ethane formation and protox inhibition. There exists an optimum length of *para*-substitutents for protox inhibition in a series of CyIs as shown in Eqn. (5), where the length effect is represented by a parabolic function of the Lp parameter. The smaller the width of the *para*-substituent, the more feasible will be the interaction with the target enzyme. The QSAR study of other series of CyI class of peroxidizers, namely N-aryl-1,5-tetramethylene-hydantoins, 4-aryl-1,2-tetramethylene-1,2,4-triazolidine-3,5-diones and their thiocarbonyl analogues, also have been demonstrated using STERIMOL parameters and Hammett σ constants (Wakabayashi, 1988; Sato *et al.*, 1992). The herbicidal activity of N-(2-fluoro-4-substituted-5-methoxy)phenyl-3,4,5,6-tetrahydrophthalimides has recently been discussed in relation to hydrophobicity constants, inductive and resonance parameters, and molar refractivity (Lyga *et al.*, 1991). It is concluded that the 4-position of the N-phenyl moiety should be occupied by a small, hydrophobic and electron-negative group for optimum activity.

The QSARs between molecular properties of 24 DPEs and their effects on protox and herbicidal activity have been reported (Nandihalli *et al.*, 1992). The QSARs indicate that the electronic (partial charge, superdelocalizability, dipole moment) and hydrophobic properties account for the variation in protox inhibition, and molecular bulk and overall electronic potentials are responsible for the herbicidal effect.

3. Peroxidizing activity and X-ray structures of peroxidizers

Nandihalli *et al.* (1992) have reported the molecular similarity between protoporphyrinogen-IX (protogen) and acifluorfen by comparing their molecular size as derived from semiempirical molecular orbital (MO) calculation. Such a comparison is feasible since protox inhibitors compete with the substrate at the target enzyme (cf. our review, part I). They reported that the maximum length (12.29 Å) and width (5.53 Å) of acifluorfen matched closely with the full length and one-half width of protogen molecule. In addition, the torsion angle of acifluorfen at the ether oxygen matched with the angle at the methylene bridge between two neighboring pyrrole rings (Fig. 5: left upper part). In our crystallographic studies, the longest length of KPP-314 (see also Fig. 2), chlorophthalim and of oxyfluorfen were 12.56 Å, 11.37 Å and 12.31 Å, respectively (Kohno *et al.*, 1993). These values indicate that the molecular size of three peroxidizing herbicides is about the same. The values 11–13 Å may indicate the length of the receptor size of protox. The torsion angles of KPP 314 and oxyfluorfen, which show good phytotoxic activity, were found approx. 65–85° also in X-ray analysis. It appears that both length and angle of the molecules have some bearing on peroxidizing activity and may contribute a steric factor to match with protox. Recent calculations based on molecular orbitals of our group have shown that cyclic imides (chlorophthalim, Fig. 5, left part, bottom) and triazolidine-type inhibitors do not match with the (b) and (c) pyrrole rings of protoporphyrinogen (as does acifluorfen), but favorably match with the (c) ring and the propanoic acid part (e). (Fujii *et al.*, 1995). The different fitting of inhibitors with protogen obviously points to different amino acid residues of protox functioning as the binding partners of these inhibitors. Lack of substantial cross-resistance between oxyfluorfen and chlorophthalim corroborates this assumption (Watanabe, 1992). Recently, Hagiwara and Nakayama (1994) have also reported the molecular similarity of three peroxidizing herbicides, namely 1,2,4-triazolin-3-one-3,4,5,6-tetrahydrophthalimide (S-23142 in Fig. 1) and 1,2,4-thiadiazoline derivatives with a 2-fluoro-4-chloro-5-propargyloxyphenyl group (NS-1556 in Fig. 9) through conformational analysis for the rotation of the phenyl ring of these compounds. We strongly suggest that molecular properties of a peroxidizing inhibitor have to be compared with those of protogen, the substrate of the enzyme. Comparison of different

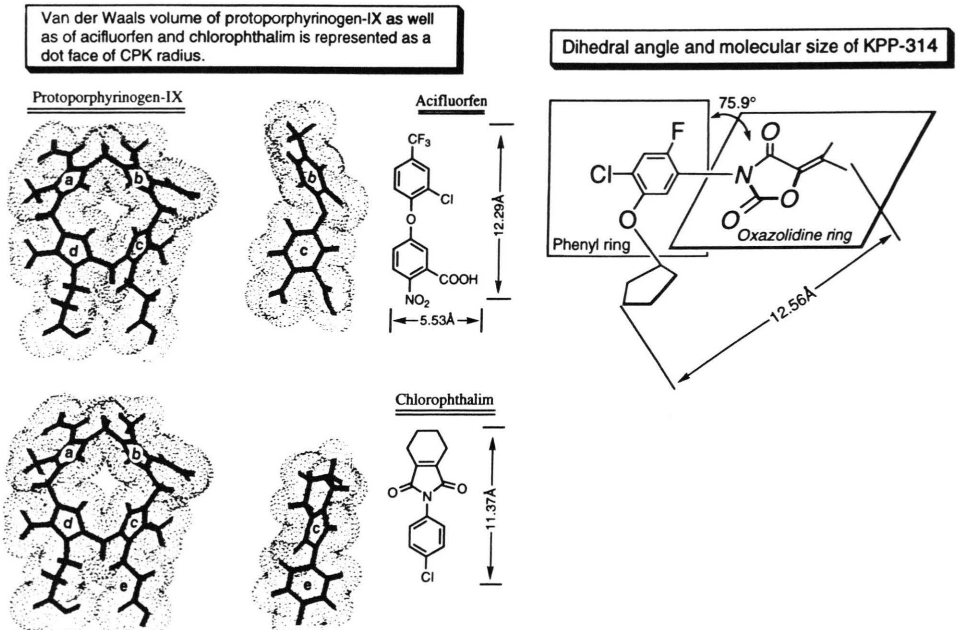


Fig. 5. Matching of peroxidizing molecules with protoporphyrinogen-IX (protogen), the substrate of protoporphyrinogen-IX oxidase: Consideration of molecular size and torsion angles in both substrate and inhibitors. Acifluorfen and chlorophthalim match best with different parts of the protogen molecule. An N-aryloxazolidinedione inhibitor (KPP-314) with its torsion angle is shown in the right part of the figure.

inhibitors alone (e.g. DPEs and cyclic imides) is not sufficient to give a clue for possible molecular design (comp. Akagi and Sakashita, 1993).

4. Structural conversion of peroxidizing herbicides in plants

The DPEs are relatively stable in the bioassay medium as compared to cyclic imides. N-Aryl-3,4,5,6-tetrahydrophthalimides (imides) and N-3,4,5,6-tetrahydrophthalamic acids (amide-acids) are interconverted to each other during incubation with seedlings of *Echinochloa utilis* (Sato *et al.*, 1991). N-Aryl-3,4,5,6-tetrahydroisophthalimides (isoimides), which show strong peroxidizing activity like imides, are transferred to amide-acids, and then the amide-acids are cyclized to imides and/or hydrolyzed to the corresponding anilines and 3,4,5,6-tetrahydrophthalic acid during a bioassay in the presence of *Echinochloa* (Fig. 6; Hoshi *et al.*, 1993). The most effective phytotoxic structures of imides, isoimides and amide-acids are now considered to be *imides* formed through the (inter)conversion mentioned above. Analogous experiments have been carried out using several sets of isomeric peroxidizing herbicides, namely 5-arylimino-3,4-tetramethylene-1,3,4-thiadiazolidine-2-ones and 4-aryl-1,2-tetra-methylene-1,2,4-triazolidin-3-one-5-thiones, exposing them to *Echinochloa* seedlings, *Scenedesmus*, or to a spinach homogenate (Hoshi *et al.*, 1992; Sato *et al.*, 1994a). The former compounds were readily converted into triazolidines, during incubation in the presence of the plants or the homogenate, however, the opposite conversion of triazolidines into thiadiazolidines was not observed. Accordingly, the most powerful phytotoxic principle of the thiadiazolidine peroxidizers appears to be due to formation of the triazolidines in the presence of plants; the triazolidines are more potent herbicides than the thiadiazolidines. Recently, it has been reported that the conversion of thiadiazolidines into triazolidines rapidly proceeds with glutathione S-transferase and SH-compounds present such as glutathione, dithiothreitol and others (Iida *et al.*, 1994a, b; Sato *et al.*, 1994b; Shimizu *et al.*, 1994, 1995). This reaction apparently reflects a new functional property of a certain glutathione S-transferase isoenzyme (Nicolaus *et al.*, 1995). The compounds, like isoimides and thiadiazolidines, can be referred to as pro-herbicides with the intention that a more active phytotoxic molecule is formed within, or in the vicinity of, plant cells, preferably at the targeted chloroplast.

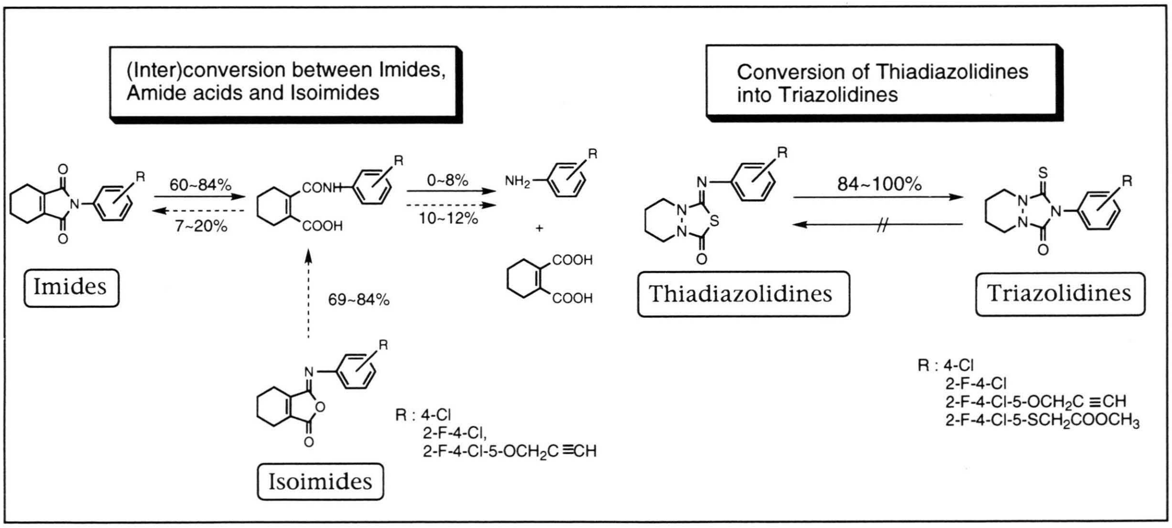


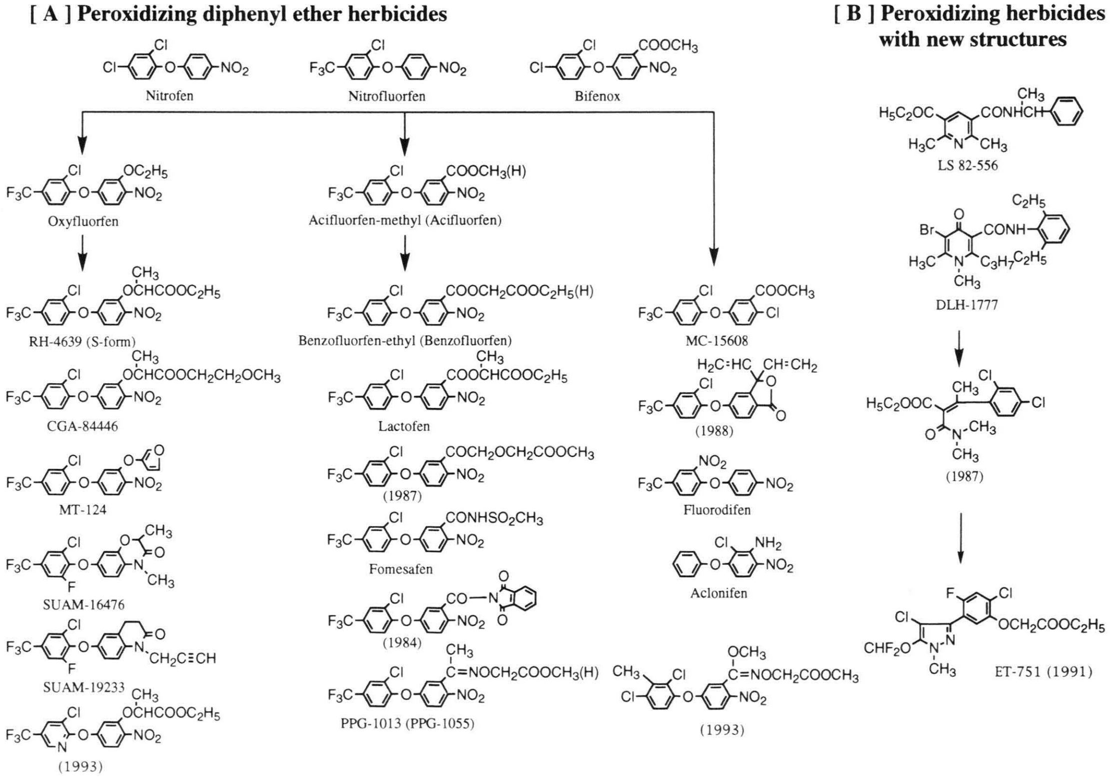
Fig. 6. Structural conversion of cyclic imide compounds (left part) and thiadiazolidines (right part) in the presence of *Echinochloa utilis* seedlings. Seedlings were cultured with the chemicals for 7 days in darkness according to Sato *et al.* (1994a). Conversion of the compounds to other structures was analyzed by HPLC.

The Second Generation of Peroxidizing Herbicides

The first generation of peroxidizing herbicides, such as oxadiazon, chlorophthalim and oxyfluorfen, have handed down their unique phytotoxic properties to more than 20 different peroxidizing herbicides or candidates of a second generation including DPEs, CyIs, pyrazoles, triazoles, triazolidines, thiadiazolidines, oxazolidines and so on, which have been developed mostly in the second half of the 1980's (Figs. 7, 8 and 9). By studies in our laboratories many of these compounds have experimentally been confirmed to be peroxidizing herbicides by inhibiting protox, causing photooxidative ethane formation and a strong bleaching effect in the light, although their structures are quite different. Some candidates, e.g. KPP-300, KPP-314, S-23142, flumipropyn, flumioxazin, fluthiacet-methyl (KIH-9201), NS-1556, thidiazimin, ET-751, PPG-1013 and SUAM-16476, are currently developed as practical herbicides. In Figures 7 to 9 these and further structures of candidates for peroxidizing herbicides are illustrated for the reader's information. Also a compilation of compounds with possible peroxidative properties written by Anderson *et al.* (1994) should be consulted. Experiments are under way to determine in detail the peroxidizing characteristics of these compounds in our laboratories.

Design for Future Peroxidizing Herbicides

The general characteristics of these herbicides are attractive features to develop a number of new target products by herbicide design. These characteristics are nowadays obtained mostly by mechanism of action studies. The inhibition of chlorophyll biosynthesis is an important mechanism of the peroxidizing action which results in decrease of plant pigments via radical reactions started by sensitized tetrapyrroles in the light. Obviously, protox is a favorable target, although it is inhibited competitively and reversibly. The low inhibitor constants for plant protox in combination with an apparent rapid turnover of proto IX to generate


[A] Peroxidizing diphenyl ether herbicides

[B] Peroxidizing herbicides with new structures

Fig. 7. Peroxidizing diphenyl ethers (A) and peroxidizing herbicides with new structures (B).

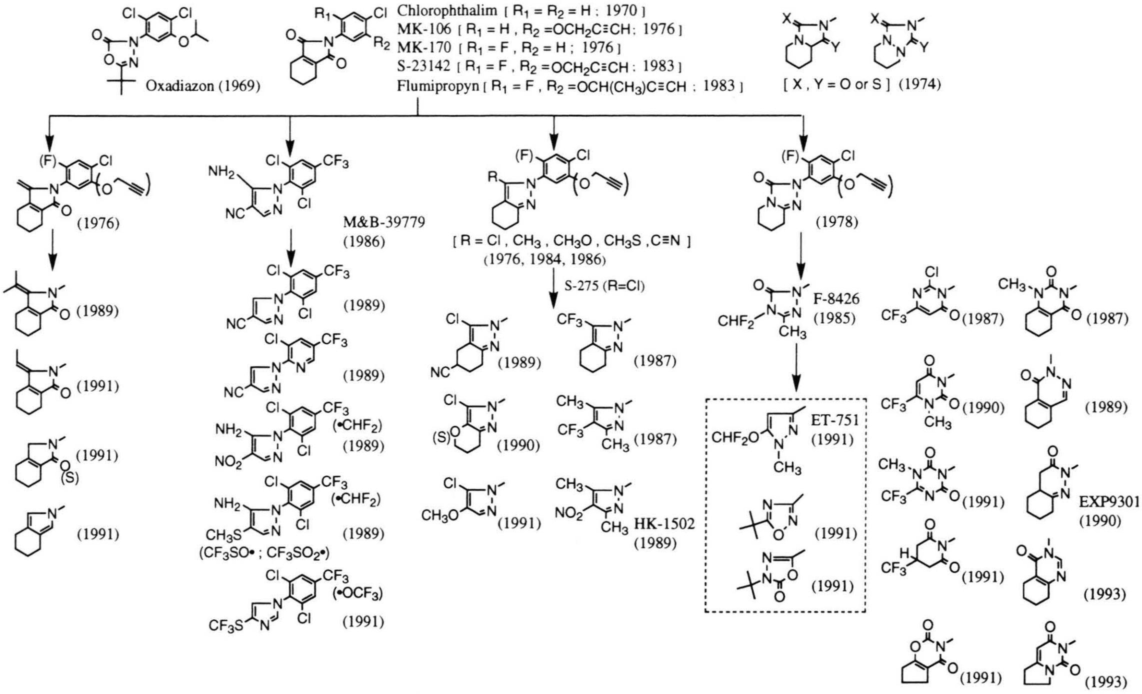


Fig. 8. Recent structural modifications of peroxidizing compounds belonging to the cyclic imide class: pyrrolidinones, pyrazoles, triazolones, pyrimidinones, pyridazinones and their analogues. For some compounds the dates are indicated when they were first patented (see also Fig. 9).

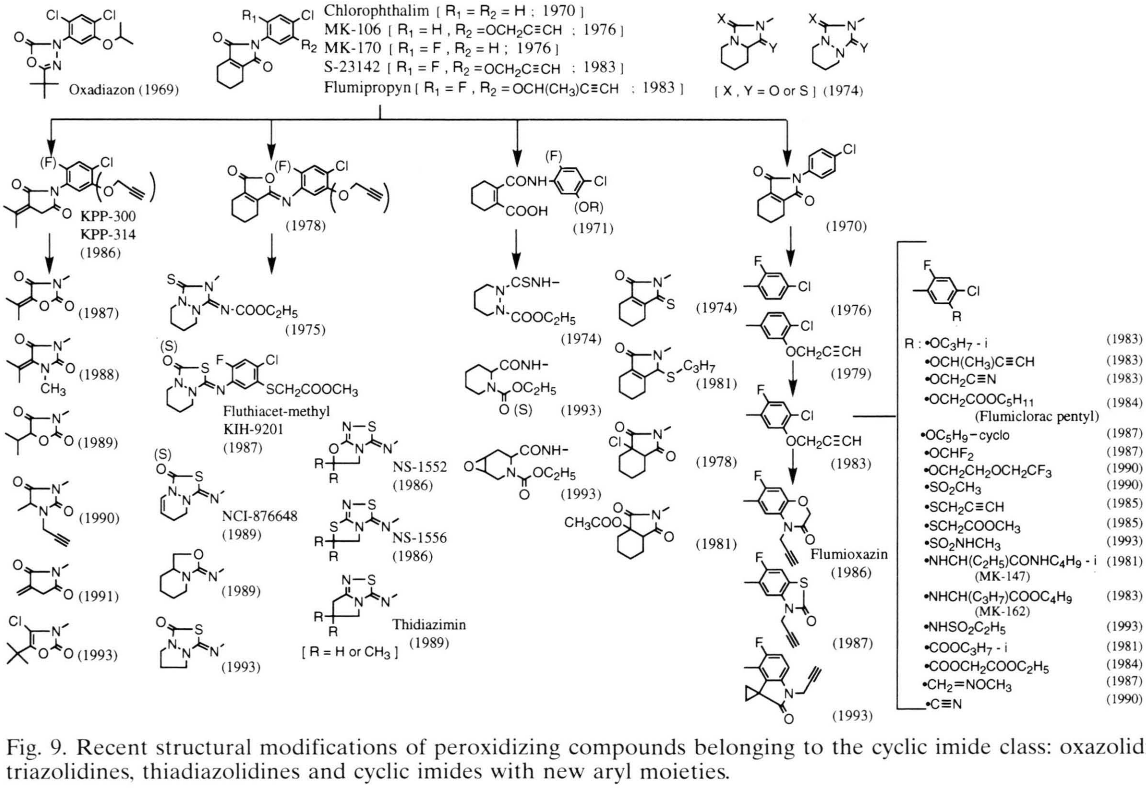


Fig. 9. Recent structural modifications of peroxidizing compounds belonging to the cyclic imide class: oxazolidines, triazolidines, thiadiazolidines and cyclic imides with new aryl moieties.

radicals lead to amazingly low use rates. These are down to some grams per hectare (e.g. 10–20 g/ha for flumipropyn or 5–10 g/ha for fluthiacet-methyl; formulas in Figs. 8 and 9, respectively), which makes such herbicidal compounds interesting candidates for future ecology-oriented chemical weed control. Leaching problems are minor ones; many of the peroxidizing herbicides in development (see Fig. 1 in Böger and Wakabayashi, 1995) exhibit a reduced persistence in soil. A variety of compounds with different core structures are good protox inhibitors giving the synthetic chemist a fair chance to find more. Prospects are good that this chance will be improved by more knowledge of the biochemistry of the peroxidation reaction system and of the enzymology involved. "Me-Too" design as well as the development of compounds with new core structures and substituents, should be based on rational approaches using advanced biochemical investigations.

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