

Chemistry and Structure-Activity Relationships of Herbicide Safeners*

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Safeners, Chemical Properties, Structure-Activity Relationships

The discovery and commercial success of safeners against thiolcarbamate herbicide injury to corn has stimulated a rapid progress and opened new possibilities for further research and development in the last decade. Compounds with new chemistry, increased efficacy, and a broader selectivity spectrum were synthesized and developed for agricultural use. Structure-activity relationship studies helped to optimize their chemical properties and to understand their biological modes of action. Several examples indicate close similarity between chemical structures possessing herbicidal and safener properties. In some cases this differentiation may be marginal, as shown in crops pretreated with low herbicide doses leading to safening effects. In other examples, however, structural optima for safening and herbicidal efficacy can be clearly differentiated.

Introduction

Traditionally herbicide safeners have been considered to have the ability to counteract phytotoxic effects of thiolcarbamates and chloroacetamides to corn (*Zea mays* L.) and sorghum [*Sorghum bicolor* (L.) Moench.] [1]. Recently developed compounds have changed this simplistic view dramatically, expanding the spectrum of safener effectivity to a variety of active ingredients (including phytotoxic fungicides) and to other crops, like rice (*Oryza sativa* L.) and wheat (*Triticum aestivum* L.) [2–5]. Higher specificity and efficacy has been achieved by the design and synthesis of safeners with rather complex chemical structures. In this paper the chemical characteristics contributing to their biological activity are reviewed.

Chemical Structures

The currently marketed crop safeners for herbicides can be classified chemically in the following groups:

- 1) naphthopyranones
- 2) dichloroacetamides
- 3) dichloromethyl acetals and ketals

- 4) oxime ethers
- 5) derivatives of 2,4-disubstituted 5-thiazolecarboxylates
- 6) substituted phenyl pyrimidines
- 7) substituted phenyl pyrazoles
- 8) quinolyloxycarboxylic acid esters
- 9) thiolcarbamates
- 10) diaryl ketones
- 11) haloalkylarylsulfones.

Chemical structures of representative safeners of the above classes and the herbicides against which they give protection in a particular crop are shown in Fig. 1.

Synthesis, Chemical and Physical Properties

Synthetic routes for the preparation of the majority of the safeners in Fig. 1 have been reviewed [1] and will not be repeated here. Further information on the chemical synthesis of different safeners is available in the literature: [6] for NA; [7] and [8] for the preparation of dichloroacetamide analogs; [9] for oxime ether derivatives; [10] and [11] for 2,4-disubstituted thiazoles; [12] for dichloromethyl ketals and acetals; and [13] for the phenylpyrimidine safener fenclorim.

Selected chemical and physical properties of the safeners introduced in the agricultural practice are listed in Table I. Most of the safeners are solids characterized with low water solubility and low vapor pressure. Interestingly, MG-191 and dichlormid are liquids with fair water solubility and relatively high volatility.

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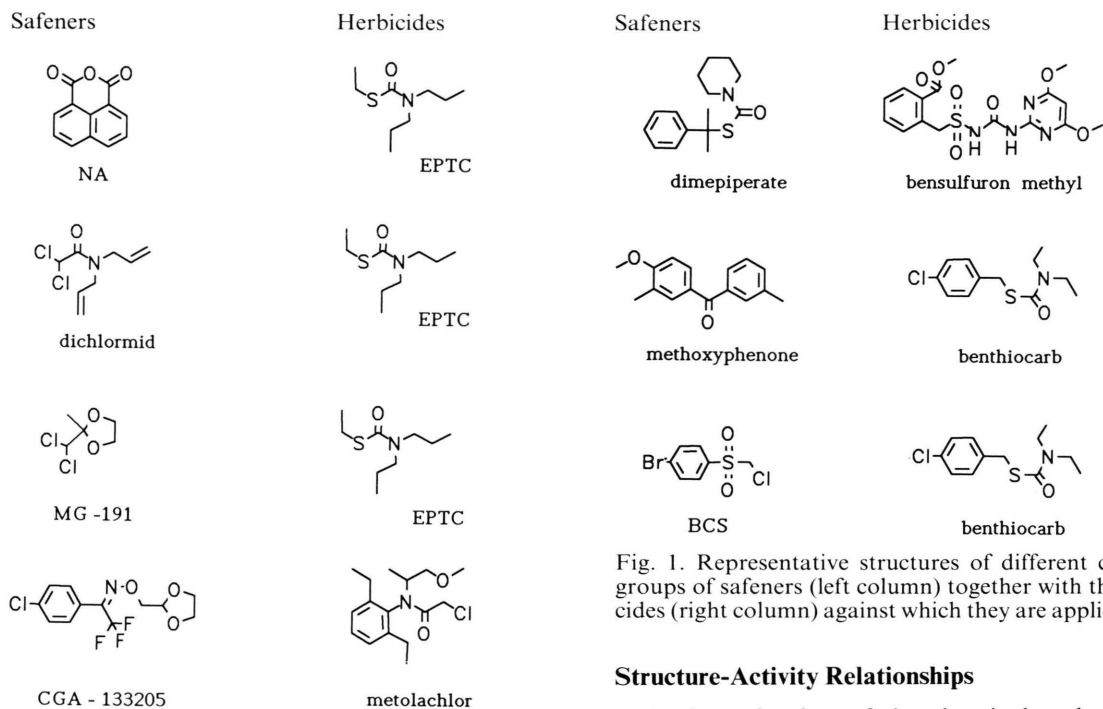


Fig. 1. Representative structures of different chemical groups of safeners (left column) together with the herbicides (right column) against which they are applied.

Structure-Activity Relationships

An investigation of the chemical and physical properties of the safeners in Fig. 1 and 2 and in Table I reveals several general patterns.

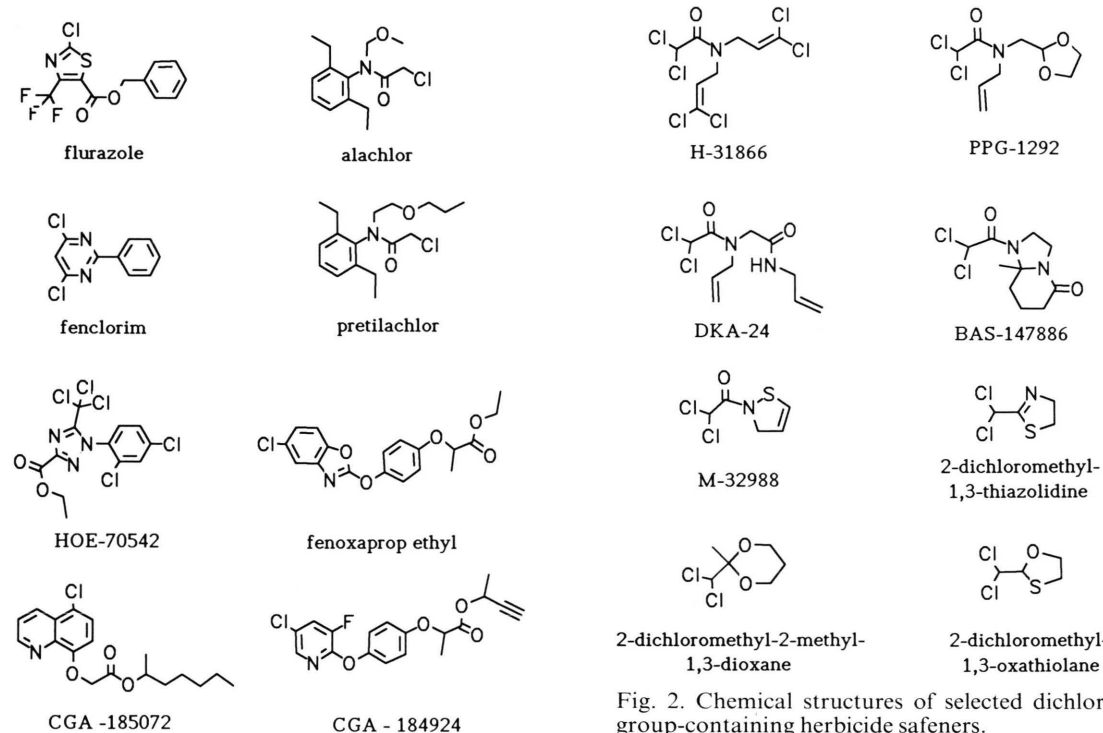


Fig. 2. Chemical structures of selected dichloromethyl group-containing herbicide safeners.

Table I. List of safeners introduced into agricultural practice.

	Common name	Chemical name	Molecular formula	MW	Physical state	Melting point [°C]
I.	Dichlormid	N,N-Diallyl-2,2-dichloroacetamide	$C_8H_{11}Cl_2NO$	208.09	liquid	
II.	NA	Naphthalene-1,8-dicarboxylic acid anhydride	$C_{12}H_6O_3$	198.18	solid	270–274
III.	Cyometrinil	(Z)-Alpha-(cyanomethoxy)-imino-benzeneacetoneitrile	$C_{10}H_7N_3O_2$	185.19	solid	55–56
IV.	Oxabetrinil	α -(1,3-Dioxolan-2-yl-methoxy)-imino-benzeneacetoneitrile	$C_{10}H_{12}N_2O_3$	232.24	solid	77–79
V.	CGA-133205	O-[1,3-Dioxolan-2-yl-methyl]-2,2,2-trifluoro-4'-chloroacetophenone-oxime	$C_{12}H_{11}ClF_3NO_3$	309.67	solid	
VI.	CGA-154281	4-Dichloroacetyl-3,4-dihydro-3-methyl-2H-1,4-benzoxazine	$C_{11}H_{11}Cl_2NO_2$	260.12	solid	107.6
VII.	CGA-185072	1-Methylhexyl-([5-chloro-8-quinolyl]-oxyacetate	$C_{18}H_{22}ClNO_3$	335.83	solid	59.3
VIII.	Fenclorim	4,6-Dichloro-2-phenylpyrimidine	$C_{10}H_6Cl_2N_2$	225.08	solid	96.9
IX.	Flurazole	Phenylmethyl-2-chloro-4-trifluoromethyl-5-thiazolecarboxylate	$C_{12}H_7ClF_3NO_2S$	321.71	solid	56–58
X.	BAS-145138	1-Dichloroacetyl-hexahydro-3,3,8- α -trimethylpyrrolo-[1,2 α]-pyrimidine-6-(2H)-one	$C_{12}H_{18}Cl_2N_2O_2$	293.20	solid	
XI.	AD-67	N-Dichloroacetyl-1-oxa-3-aza-spiro-4,5-decane	$C_{10}H_{15}Cl_2NO_2$	252.14	solid	106
XII.	HOE-70542	Ethyl-1-(2,4-dichlorophenyl)-5-trichloromethyl-1H-1,2,4-triazole-3-carboxylate	$C_{12}H_8Cl_5N_3O_2$	403.48	solid	108–112
XIII.	MG-191	2-Dichloromethyl-2-methyl-1,3-dioxolane	$C_5H_8Cl_2O_2$	171.02	liquid	
XIV.	Dimepiperate	N-(1,1-Dimethylbenzylthio-thiocarbonyl)-piperidine	$C_{15}H_{21}NOS$	263.40		
XV.	Methoxyphenone	3,3'-Dimethyl-4-methoxy-benzophenone	$C_{16}H_{16}O_2$	240.30	solid	62.0–62.5
XV.	BCS	Chloromethyl-4-bromophenyl sulfone	$C_7H_6BrClO_2S$	269.55		

* Estimated by computer program ProLogP 4.1 (CompuDrug Ltd., Budapest, Hungary) [14].

Table I. (Continued)

	Method of application	Protected plant	Vapor pressure [Hg mm]	Water solubility at 20 °C [mg/l]	log P*	Patented by
I.	Tank mix	corn	6.0×10^{-3} (25 °C)	5000	2.063	Stauffer Chem. Co.
II.	Seed dressing	corn		<2	2.438	Gulf Chem. Co.
III.	Seed dressing	sorghum		95	1.161	Ciba-Geigy Ltd.
IV.	Seed dressing	sorghum	5.2×10^{-4} (25 °C)	20	1.018	Ciba-Geigy Ltd.
V.	Seed dressing	sorghum		10	3.292	Ciba-Geigy Ltd.
VI.	Tank mix	corn	4.4×10^{-6} (20 °C)	20	3.296	Ciba-Geigy Ltd.
VII.	Tank mix	wheat	2.5×10^{-6} (20 °C)	0.8	7.312	Ciba-Geigy Ltd.
VIII.	Tank mix	rice	9.0×10^{-5} (20 °C)	2.5	3.055	Ciba-Geigy Ltd.
IX.	Seed dressing	sorghum	3.8×10^{-5} (25 °C)		5.226	Monsanto Co.
X.	Tank mix	corn		30	1.789	BASF Ltd.
XI.	Tank mix	corn		328	3.625	Nitrokemia Co.
XII.	Tank mix	wheat	6.7×10^{-9} (20 °C)	0.9	7.144	Hoechst Ltd.
XIII.	Tank mix	corn	3.2×10^{-1} (20 °C)	9730	1.503	Nitrokemia Co.
XIV.	Tank mix	rice			3.469	Du Pont Co.
XV.	Tank mix	rice			4.397	Kumiai Co.
XVI.	Tank mix	rice			2.366	Kumiai Co.

a) Structural similarities between a herbicide and its safener are evident in the case of EPTC and dichlormid (Fig. 1). This observation has been further supported by structure-activity investigations [8, 15] and molecular graphic studies [16]. The simplest explanation for this apparent similarity may be a possible competitive antagonism between the thiolcarbamate herbicide and the safener molecules for a common target site [8, 16, 17]. It is interesting to note that herbicidal thiolcarbamates may function as safeners against injury by a structurally unrelated sulfonyl urea, bensulfuron methyl [2].

b) The possibility exists that similarities in the physical properties of a safener to those of the herbicide against which it gives protection may also be beneficial. Though the scarce availability of data in this respect does not allow a firm conclusion, it is interesting to note that the "outliners" in Table I (MG-191 and dichlormid, liquids of relatively low lipophilicity [log P], high water solubility and vapor pressure) are safeners tailored to give maximum protection against injury by EPTC and related thiolcarbamates. Indeed, dichlormid and MG-191 have physical properties quite similar to those of the aliphatic thiolcarbamates. These herbicides and their safeners may act at the same site of action [17] and are thought to be taken up by the same crop plant tissue from the vapor phase [18].

c) With the exception of NA all corn safeners contain a dichloromethyl group, show protective action against thiolcarbamates and chloroacetanilides, and are applied in a mixture with the herbicide.

d) In sorghum only seed safeners proved to possess sufficient activity. Their chemical structures, unlike those active in corn, do not seem to have common features.

e) Safeners developed to protect wheat are solids, of remarkably high lipophilicity, low water solubility, and low vapor pressure.

f) An investigation of the chemical structures of the known safeners reveals the importance of the presence of at least one electrophilic center in their molecules. This center may be a carbon atom of an *oxo* function (in NA, dichloroacetamides, CGA-185072, flurazole, dimepiperate, and HOE-70542) or of a haloalkyl group (in BCS, dichloromethyl group-containing safeners), an aromatic carbon in a heterocyclic ring (in fenclorim, CGA-185072,

HOE-70542), or a carbon-carbon double bond bridging two carbonyl groups (in derivatives of maleic acid). Possible reaction partners attacking these electrophilic centers may be (macro)molecules with sulfhydryl group(s) [19, 20]. Though in some cases such chemical transformations of safeners ("conjugation reactions") were clearly demonstrated [19], information on such nucleophilic substitutions by sulfhydryls on dichloromethyl group-containing safeners (with or without oxidative bioactivation) are only circumstantial [20]. The products of these transformations ("conjugates") may have direct or indirect roles in the regulation of the defense mechanisms of plants against phytotoxic chemicals [19, 20].

Altering the chemical structure of a safener may lead to significant changes in its biological activity, resulting in increased or decreased protective ability or even considerable phytotoxicity to the crop plant [2].

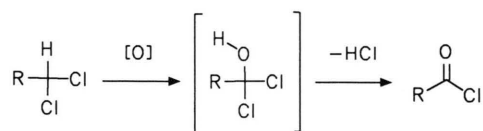
The number of publications on structure-activity relationships (SAR) of herbicide safeners is low, though selected data on SAR studies carried out with safeners in industrial laboratories are available from the patent literature. For example, in the patent description of NA [21] safening action of eight additional derivatives on corn are given against the thiolcarbamate herbicide EPTC. Further data on the safening efficacy of nine structural analogs of NA on corn against EPTC injury in the greenhouse were published in a recent paper by Hatzios and Zama [22]. They showed that the presence of the dicarboxylic anhydride group and at least one aromatic ring attached directly to the anhydride is essential for the exhibition of corn safening activity by these structural analogs of NA against EPTC injury to corn. Some of the analogs inhibited germination of corn seeds and induced toxic symptoms, *e.g.*, introduction of a chlorine atom in the 6-position of NA increased the phytotoxicity of NA by causing chlorosis and stunting in corn seedlings grown from seeds treated with this analog [22].

Most of the SAR studies published on safener action evaluate acetamides as protectants against thiolcarbamate herbicide injury to corn [8, 15, 23, 24]. From these works it is evident that the N,N-disubstituted dichloroacetamides are the most active derivatives, while mono- and trichloroacetamides as well as N-monosubstituted dichloro-

acetamides are much less effective. The diallyl-amino portion of dichlormid may be replaced with open, cyclic and bicyclic units leading to derivatives of lower vapor pressure, extended availability for plant uptake, and still retain the features essential for safener activity in corn (Fig. 1 and 2). Substituents at the nitrogen atom determine the spectrum of biological action of the compound. Therefore, in addition to safening action against thiolcarbamates, dichloroacetamides like CGA-154281 a substituted dichloroacetyl-1,4-benzoxazine [25] and AD-67 a spiro-compound [26] were established as effective safeners of corn against chloroacetanilide herbicide injury (Fig. 1).

In contrast to the high variability of the N-substituents, at the acyl portion the presence of the dichloromethyl moiety was found to be an absolute necessity [2, 8, 15, 24]. Interestingly, optimum activity for ketal (MG-191), oxathiolane and oxazoline safeners (Fig. 1) was also found when the 2-position of the molecule was occupied by a dichloromethyl group [2, 15, 27] suggesting the involvement of a common mechanism in the biochemical mode of action of dichloroacetamides, ketals, oxathiolanes and oxazolines. The apparent importance of the dichloromethyl moiety in all the highly active amide type safener molecules in corn against thiolcarbamate and chloroacetanilide herbicide injury in corn has been interpreted in differ-

ent ways. Based on experiments with amides, as well as with esters, ketones and thioesters containing the dichloroacetyl group, an involvement of a transacylation reaction in the biological action of these safeners was proposed [20]. A suicide enzyme inhibition reaction by dichloromethyl group-containing safeners was also suggested [20]. This reaction, similarly to the bioactivation of chloramphenicol in mammalian systems [28], would involve an oxidative dechlorination of the dichloromethyl group to yield an unstable intermediate. This, in turn, would spontaneously liberate hydrogen chloride to produce a highly reactive acyl chloride according to Eqn. (1). Acylation by this acid chloride product of an enzyme active site in which it is formed and/or of other sites would then result in biological action.



Of various acetals with open structures investigated, optimal, though modest safening activity against thiolcarbamates and chloroacetanilides in corn was associated with the diethylacetal of dichloroacetaldehyde (Table II). As indicated above, derivatives of acetaldehyde and of mono- or tri-

Table II. Safener activity of selected analogs of MG-191 against thiolcarbamate and chloroacetanilide herbicide injury to corn in sand culture*.

Compound No.	R ¹	R ²	R ¹ R ² C(OR ³)(OR ⁴)		Activity
			R ³	R ⁴	
1	-CH ₃	-H	-CH ₂ CH ₃	-CH ₂ CH ₃	inactive
2	-CH ₂ Cl	-H	-CH ₂ CH ₃	-CH ₂ CH ₃	poor
3	-CHCl ₂	-H	-CH ₂ CH ₃	-CH ₂ CH ₃	moderate
4	-CCl ₃	-H	-CH ₂ CH ₃	-CH ₂ CH ₃	inactive
5	-CHCl ₂	-H	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	good
6	-CHCl ₂	-CH ₃	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	excellent
7	-CHCl ₂	-CH ₃	-CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ -	excellent
8	-CHCl ₂	-CH ₃	-CH ₂ CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ CH ₂ -	poor
9	-CHCl ₂	-CH ₂ CH ₃	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	good
10	-CHCl ₂	-C ₆ H ₅	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	good
11	-CHCl ₂	-CH ₃	-CH ₂ CH(CH ₃)-	-CH ₂ CH(CH ₃)-	good
12	-CHCl ₂	-CH ₃	-CH(CH ₃)CH(CH ₃)-	-CH(CH ₃)CH(CH ₃)-	moderate
13	-CHCl ₂	-CH ₃	-CH(CH ₃)CH ₂ CH ₂ -	-CH(CH ₃)CH ₂ CH ₂ -	moderate
14	-CHCl ₂	-CH ₃	-CH ₂ CH(CH ₃)CH ₂ -	-CH ₂ CH(CH ₃)CH ₂ -	moderate

* Thiolcarbamates: EPTC, vernolate, butylate. Chloroacetanilides: acetochlor, alachlor, metolachlor. Corn hybrids: Pioneer 3732, 3737, 3901, and 3950. For experimental see [3].

chloroacetaldehyde were yet less potent safeners. As a result of further syntheses and bioassays it quickly became evident that 5- and 6-membered cyclic acetals of dichloroacetaldehyde (1,3-dioxolanes and 1,3-dioxanes) exhibit higher safening potency. Increasing the ring size to 1,3-dioxepine structure resulted in a less active derivative. Maximum safener activity was achieved by introducing an alkyl substituent into the 2-position of the dioxolane or the dioxane ring (Fig. 2) [27].

Investigations of safening efficiency of oxime ether derivatives by Chang and Merkle [29, 30] showed that it depends on the number of nucleophilic sites that are present in the molecule: an increase in the number of nucleophilic sites from one to two leads to a more active safener. Development of new safeners from this class of compounds seems to be continuous with the recent introduction of CGA-133205 [31].

SAR studies with 2,4-disubstituted 5-thiazole-carboxylates have been reported by Howe and Lee [10]. Highest safening activity for protecting sorghum against chloroacetamide herbicide injury was found for thiazole alkyl esters with a chlorine atom at the 2-position and a trifluoromethyl group at the 4-position of the thiazole ring. From this group, flurazole was chosen for commercial development.

An SAR investigation by Rubin *et al.* [32] was reported on aryl-substituted N-phenylmaleimides, isomaleimides and maleamic acids (Fig. 3). It was concluded that maleimides and isomaleimides are “prosafeners” and are converted in the plant tissue to the maleamic acid form, which is responsible for safening action. Biological activity was strongly influenced by substituents on the aryl portion and was determined primarily by the steric parameters of the molecules [32]. Though structural similarity between safener [32] and herbicidal [33] imides is apparent (Fig. 3), structure optima are remarkably different: for example, bicyclic dicarboxylic acid imides are excellent herbicides [34], but poor safeners [32]. Substitution in the 3-position of their benzene ring leads to reduced safening ability [32], but is essential for maximum herbicidal effect [33].

A “prosafener” of different nature was described by Hilton and Pillai [35]: L-2-oxothiazolidine-4-carboxylic acid (OTC) is enzymatically transformed to S-carboxy-L-cysteine, which spontaneously yields L-cysteine, according to the Eqn. (2). OTC was found to increase the non-protein

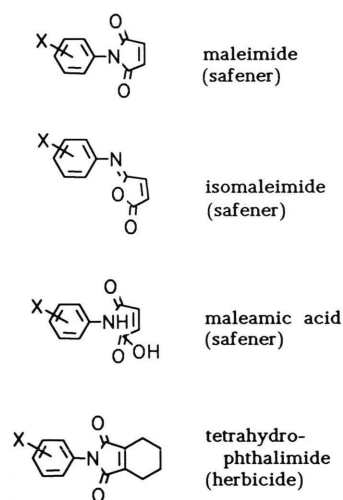
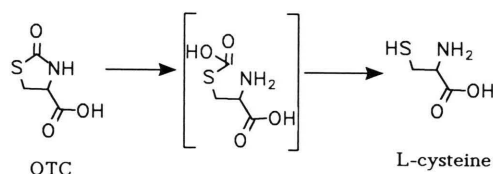


Fig. 3. General structures of safener and herbicidal maleic acid derivatives and analogues.

sulfhydryl content of corn seedlings above that of the controls and act as a safener against the phytotoxic action of the herbicide tridiphan (2-[3,5-dichlorophenyl]-2-[2,2,2-trichloroethyl]oxirane) [35].

Chemical structures of several recently commercialized herbicide safeners are also shown in Fig. 1. Fenclorim [13], BCS [2], and dimepiperate [2] have been introduced to protect rice against injury by chloroacetanilide, thiocarbamate, and sulfonyl urea herbicides, respectively. HOE-70542 was recently developed by the chemical company Hoechst to protect wheat against damage by the herbicide fenoxaprop [5], while CGA-185072 protects this crop plant against injury by the chemically similar aryloxyphenoxy acid ester herbicide CGA-184927 [4]. Unfortunately, information on SAR studies with these novel classes of herbicide safeners is not available.

Conclusions

Our knowledge on the effects of chemical structural modifications on the biological activity of herbicide safeners has expanded greatly in recent years. The importance of structural similarity between a herbicide and its safener(s) has been shown to be advantageous but not an absolute necessity for efficient protective action. Recent studies demonstrated the requirement of at least one

electrophilic site in molecules of herbicide safeners available for possible nucleophilic displacement reactions. A major question needing further clarification is the possible role of safener conjugates with glutathione and/or other endogenous sulfhydryl containing (macro)molecules in the safener action, and the elucidation of structural requirements for optimum activity of such conjugates.

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