4

Enantioselective Activity and Toxicity of Chiral Herbicides

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1. Introduction

Chirality is a natural property that is well known to chemists and has been generally recognized in the life sciences since Pasteur discovered the optical isomers of tartrate and van't Hoff and LeBel proposed the theory of the stereostructure of carbon compounds (GassmannKuo & Zare, 1985; Koeller & Wong, 2001; KondruWipf & Beratan, 1998). Almost all of the biological macromolecules, such as DNA, RNA, protein, polynucleotides, and even the amino acids, the basic structural units of life, are chiral(Roelfes, 2007). Although the enantiomers of chiral substances have the same physicochemical properties, their biochemical activities, unlike abiotic transformations, can be quite different because biochemical processes usually show high stereo- or enantioselectivity (Muller & Kohler, 2004). For instance, enantioselective reactions occur in biological enrichment(Hegeman & Laane, 2002), degradation and other physiological actions(Wong, 2006). For organisms, enantiomers often exhibit different effects or toxicities. The "active" enantiomer of a chiral chemical may have the desired effect on a target species, whereas the other enantiomer may not(Garrison, 2006). It is advisable to use only the biologically active enantiomers, thereby reducing the total amount of chemical pollutants released into the environment.

Many commercial agrochemicals have chiral structures. For example, about 30% of currently registered pesticide active ingredients contain one or more chiral centers(Sekhon, 2009). Herbicides are used to control the growth of undesired vegetation, and they account for most of the agrochemicals in use today. Some chiral herbicides are sold as purified, optically active isomers, but for economic reasons, many others are still used as racemates. Different enantiomers of chiral herbicides can have different enantioselective activities on target weeds and different toxic effects on non-target organisms because of their enantioselective interactions with enzymes and biological receptors in organisms(Yoon & Jacobsen, 2003). Although the high efficiency and environmental safety of herbicides are of great concern, studies on their enantioselective activity and toxicity are still limited. It is very important to pay attention to the effects of chiral herbicides on biological systems in future research in order to achieve efficient, green, safe and pure herbicides with chirality, to make regulatory decisions and to predict the environmental risks of such herbicides.

This review summarizes the activities of different kinds of chiral herbicides that are widely used, such as phenoxyalkanoic acids, aryloxyphenoxypropionates, acetanilides, ureas, diphenyl ethers and other herbicides. It also address different types of enantioselective

toxicity, including chronic toxicity, acute toxicity, and phytotoxicity. The enantioselective properties of the interactions between chiral herbicides and biological macromolecules via models in vivo or in vitro are also discussed. In further researches, finding low-cost methods for separating the enantiomers of herbicides to produce potent enantiopure herbicides, considering both the degradation and toxicity of the herbicides when assess chiral herbicides and exploring the mechanism of the interaction between chiral herbicides and receptors seem significant.

2. Enantioselective activities of chiral herbicides on target plants

The configurations of chiral herbicides are often strongly affect their biological activities. Often, only one enantiomer is target-active, or one is more target-active than the other, in which case the inactive or less active enantiomer simply contributes to the chemical load that pollutes the environment(Garrison, 2006). The activity of chiral herbicides on plants is always enantioselective because individual stereoisomers can interact differently with other chiral molecules, such as enzymes and other biological receptors(Wong, 2006), and the processes of absorption, interaction of target enzymes and metabolism are affected differently by different enantiomers. As a consequence, some enantiomers show higher activity against weeds, and others show lower activity. Because chiral herbicides have the advantages of high-efficiency and universal applicability, the technical separation of racemates or the synthesis of pure or enriched enantiomers is of growing importance for the agrochemical industry. Early in 1974, the chemical company BASF in Germany brought the enantiomerically pure chemical mecoprop-P (Fig. 1) to market, and after that, dozens of pure or enriched chiral herbicides were produced and applied successfully (Zipper, Nickel, Angst, & Kohler, 1996).

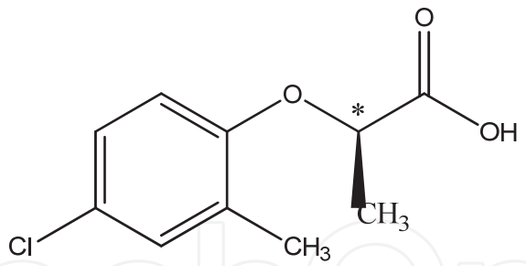


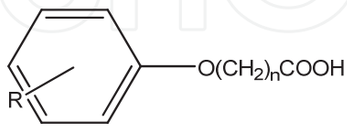
Fig. 1. Chemical structure of mecoprop-P (*R*-2-(4-chloro-2-methylphenoxy)propionic acid).

2.1 Phenoxyalkanoic acids

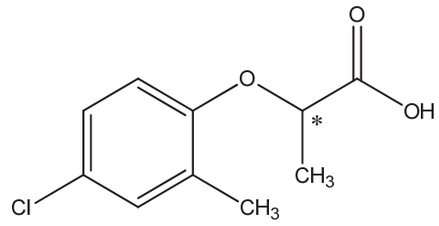
The phenoxyalkanoic acids (Fig. 2) comprise an important set of organic compounds, of which several halogenated analogues are commercially available as auxin or "hormone" herbicides(Kennardsmith & White, 1982). They are widely used to control broadleaf weeds in agriculture, lawn care, and industrial applications. Phenoxyalkanoic acid herbicides work by inhibiting acetyl-CoA carboxylase(ACCase), which leads to the termination of fatty acid synthesis, abnormal cell growth and division, and, ultimately, suppression of weed growth.

The most significant chiral compounds that have been commercialized are mecoprop and dichlorprop. Mecoprop and dichlorprop are chiral molecules that each have one stereogenic center and, therefore, exist as two enantiomers(Muller, Fleischmann, van der Meer, &

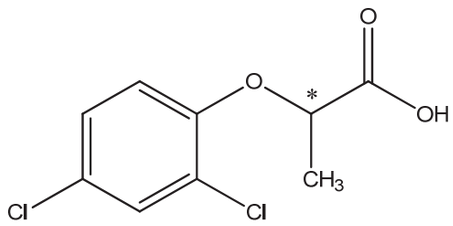
Kohler, 2006). As early as 1953, it was reported that the *R*-enantiomers have herbicidal activity, and the *S*-enantiomers have little observable activity(Matell, 1953). Authorities in the Netherlands and Switzerland have revoked registrations for racemic mixtures of chiral phenoxy herbicides while approving registrations of single-isomer products (named mecoprop-P and dichlorprop-P)(W. P. Liu, J. Ye & M. Q. Jin, 2009). In plants, mecoprop and dichlorprop were found to be enantioselectively degraded in a study conducted by Schneiderheinze. The *S*-(-)-enantiomer of each herbicide was preferentially degraded in most species of broadleaf weeds, whereas the *R*-(-)-enantiomer of each herbicide was more resistant to degradation(Schneiderheinze, Armstrong & Berthod, 1999).



R=phenoxy, aryloxy or aromatic heterocyclicoxyl; n=1, 2 or 3.
Phenoxyalkanoic acids



Mecoprop
(2-(*R*,*S*)-2-methyl-4-chlo-rophenoxypropanoic acid



Dichlorprop
(2-(*R*,*S*)-2,4-dichlo-rophenoxypropanoic acid)

Fig. 2. Chemical structures of phenoxyalkanoic acids*; asymmetric carbon.

2.2 Acetanilides

The chirality of acetanilide herbicides (Fig. 3) is caused by the presence of two asymmetric carbons and two chiral axes that generate two pairs of enantiomers, and the herbicide activity is mainly attributed to the *S*-enantiomer of the carbon in the alkyl substituent. The *S*-enantiomers of the herbicides metolachlor (Schmalfuss, Matthes, Knuth, & Boger, 2000) and dimethenamide (Couderchet, Bocion, Chollet, Seckinger, & Boger, 1997; Gotz & Boger, 2004) were reported to inhibit fatty acid synthase. Using acyl-CoA as a substrate to test the activity of the chiral chloroacetamide metolachlor, it was shown that only the herbicidally active *S*-enantiomer could inhibit elongation, whereas the *R*-enantiomer had no effect (Schmalfuss et al., 2000). When 5 μmol/L dimethenamid *S*-enantiomer was applied, the algal growth and fatty acid desaturation were strongly inhibited, but the *R*-enantiomer had almost no effect on algal growth (Couderchet et al., 1997). Also, the inhibition of protein synthesis and RNA polymerase I activity was found to occur as part of the active mechanism of acetanilides (Chesters et al., 1989; Liu et al., 2009).

Metolachlor is a widely used herbicide that inhibits the synthesis of fatty acids in broadleaf weeds. In 1982, it was found that the two 1*S* stereoisomers of metolachlor provide most of its biological activity. The herbicidal activity of the *S*-enantiomers was almost 10 times higher than that of the *R*-enantiomers (Blaser et al., 1999; Fayez & Kristen, 1996). Their activity is mainly influenced by the configuration at the chiral centre, a carbon in one of the

alkylic substituents of the nitrogen in the imide group, and by the atropisomerism generated by the hindered rotation around the aryl carbon-nitrogen bond (Polcaro et al., 2004). A systematic experiment found that acyl-CoA elongation was only inhibited by the herbicidally active *S*-enantiomer, whereas the *R*-enantiomer had no influence. Furthermore, enzyme activity could not be recovered by dilution of the enzyme-inhibiting chiral herbicide(Schmalfuss et al., 2000).

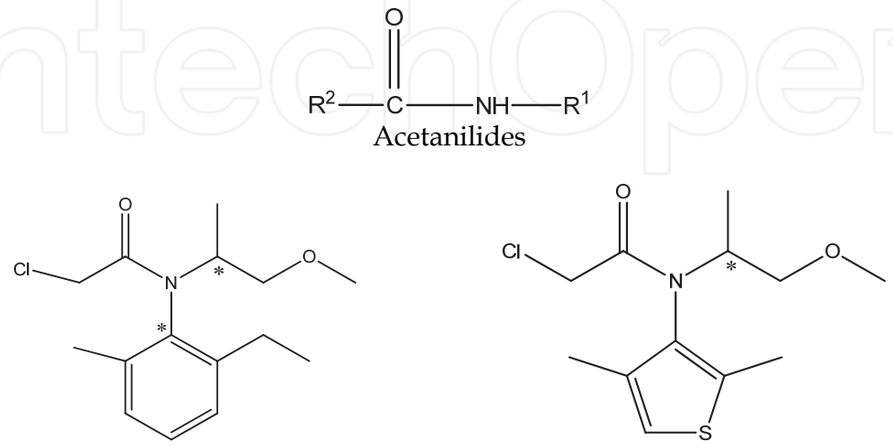


Fig. 3. Chemical structures of acetanilides.

2.3 Aryloxyphenoxypropionates

Aryloxyphenoxypropionates (AOPP) are postemergence herbicides that cause almost immediate growth inhibition in the shoot, root and intercalary meristems. Diclofop-methyl, fluazifop-P, haloxyfop-methyl, fenoxaprop-P-ethyl, quizalofop-ethyl, Fenthiaprop, and fenoxaprop-P- ethyl (Fig. 4) are all examples of chiral AOPP herbicides. A wide variety of AOPPs and their esters have been developed as commercial herbicides. Recent studies indicate that the mechanism controlling the growth of grasses by this kind of herbicide is the same as that of phenoxyalkanoic acids: they interfere with lipid metabolism in susceptible plants and inhibit the plastid ACCase, a key enzyme in long-chain fatty acid biosynthesis (Kunimitu et al., 1988; Liu et al., 2009). Chiral AOPPs have enantioselective activity on target plants. Their herbicidal activity comes almost entirely from the *R*-enantiomers rather than the *S*-enantiomers, which means that the *R*-enantiomers are more effective than the *S*-enantiomers for weeding (Sakata et al., 1985). Many reports have described the enantioselective activity of AOPPs on target weeds.

Both enantiomers of diclofop-methyl show similar pre-emergence herbicidal activity for controlling weeds in the rice field, but in postemergence applications, the *R*-(+)-isomer has higher activity against millets and oats. The most likely mechanisms of action for diclofop-methyl were discussed in the context of its role in oxidative membrane catabolism by free radical lipid peroxidation and its coupling to the effect of diclofop on the transmembrane proton gradient (Kurihara et al., 1997; Shimabukuro & Hoffer, 1995). Racemic mixtures and

(+)-AOPP are active in alfalfa embryo induction, whereas the (-)-forms are inactive and do not inhibit embryogenesis (Stuart & Mccall, 1992).

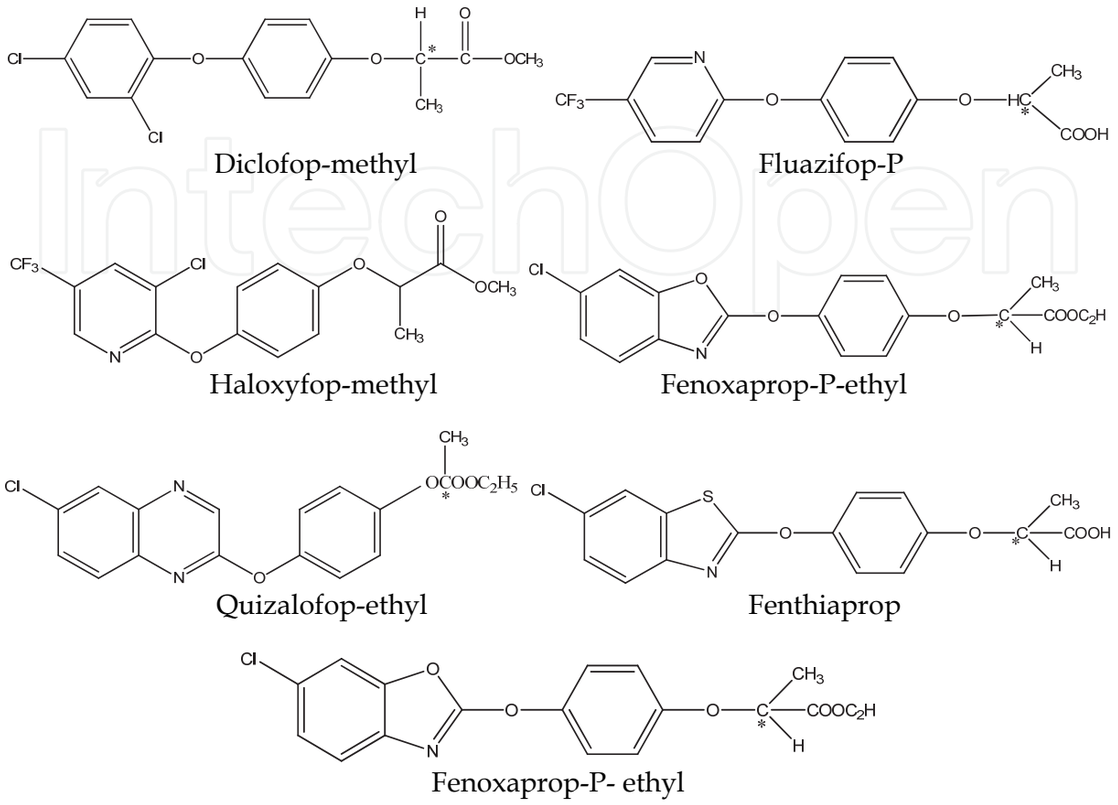
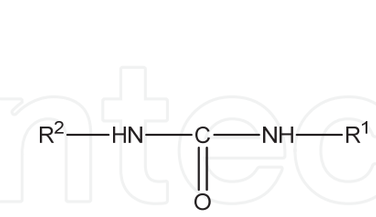


Fig. 4. Chemical structures of aryloxyphenoxypropionates.

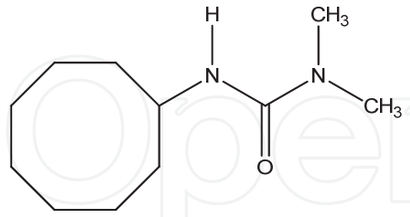
2.4 Ureas

The key structural feature of substituted urea herbicides (Fig. 5) is the urea moiety, and different substituents of the amino groups produce various kinds of urea herbicides. The action of this kind of herbicide depends on differences in absorption, conduction and degradation abilities between plants and weeds. Ureas act by inhibiting the Hill reaction in photosynthetic electron transport (Jurado et al., 2011). Cycluron, daimuron and clodinafop-propargyl are the main brands of urea herbicides. Of these, daimuron and *R*-clodinafop-propargyl are the ones that have been commercialized. Daimuron has a very plant-specific effect: it shows herbicidal activity against paddy weeds. The *R*-enantiomer inhibits the growth of *Cyperaceae* weeds more strongly than the *S*-enantiomer (Ryoo et al., 1998; Omokawa et al., 1999). The herbicide 1-α-methylbenzyl-3-p-tolyl urea (MBTU), a derivative of daimuron, was shown to have enantioselective differences in potency. For instance, it was reported that the enantiomers of MBTU have different depression effects on roots in a number of *Oryzeae*, *Echinochloa* and wheat species, and the root growth of all members of the genus *Oryza* was inhibited more strongly by *R*-MBTU than by *S*-MBTU. In contrast, the root growth of *Echinochloa* and wheat was more sensitive to *S*-MBTU than to the antipodal *R*-MBTU (Omokawa et al., 2004; Kazuhiro et al., 2009). Imai et al. thought that the decrease in free amino levels in the root tips was the reason that *R*-/*S*-MBTU inhibited the growth of the

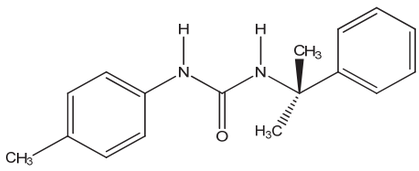
plants (Imai, Kojima & Numata, 2009). The activity of α-methylbenzyl-p-tolylureas (4-Me) mainly depends on the substituents of benzene. The 4-Me *R*-enantiomers with a smaller alkyl group exhibited significant activity on both of the plant species on which they were tested (Omokawa & Ryoo, 2001).



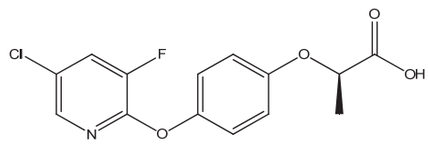
Ureas



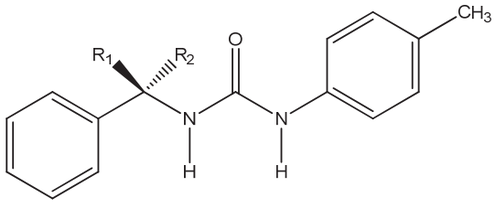
Cycluron(1,1-Dimethyl-3-cyclooctylurea)



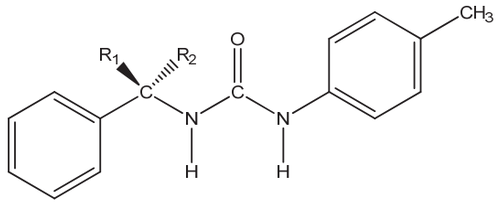
Daimuron
(N-(4-Methylphenyl)-
N'-(1-methyl-1-phenylethyl)urea)



clodinafop-propargyl
(*R*-2-[4-[(5-chloro-3-fluoro-2-
pyridinyl)oxy]phenoxy]propanoic acid)



R-MBTU:R_1=CH_3,R_2=H;
S-MBTU:R_1=H,R_2=CH_3



R-4-Me:R_1=CH_3,R_2=H;
S-4-Me:R_1=H.R_2=CH_3

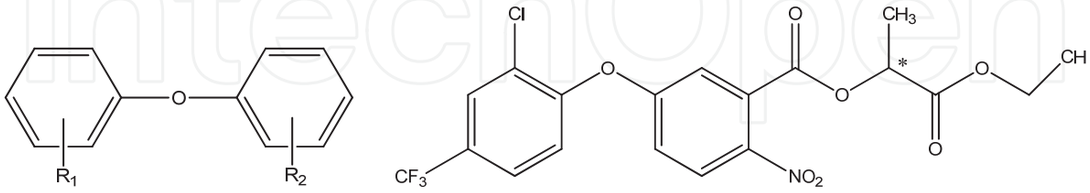
Fig. 5. Chemical structures of ureas.

2.5 Diphenyl ethers

Diphenyl ethers (Fig. 6) can inhibit the photosynthesis and affect the composition of chloroplasts, thereby causing the death of weeds. Among diphenyl ether herbicides, nitrodiphenyl ethers have a chiral structure and are used to control broadleaf weeds. They are able to cause light-dependent membrane lipid peroxidation, and their *S*-(-)-enantiomers have been shown to be substantially more active than their *R*-(+)-enantiomers in a test designed to monitor plant membrane breakdown by Camilleri et al. This finding presumably reflected the fact that the binding of nitrodiphenyl ethers to a metabolic enzyme in plants is enantioselective. Nitrodiphenyl ethers and their analogues act by increasing the level of protoporphyrin IX in an enantiotopically specific active site by inhibiting an enzyme in the biosynthetic pathway between protoporphyrin IX and protochlorophyllide (Camilleri et al., 1989). A test using the green alga *Chlamydomonas reinhardtii* as an indicator species showed that 5-[2-chloro-4-(trifluoromethyl)phenoxy]- 3-nitroacetophenone oxime-*O*-(acetic acid, methyl easter) (DPEI), also a type of nitrodiphenyl ether herbicide, had enantioselective activity. The purified *S*-(-)-enantiomer had greater herbicidal activity than

the *R*-(+)-isomer, and the mechanistic reason was that the *S*-(-)-enantiomers of DPEs had greater potency in inhibiting protoporphyrinogen IX oxidase (Hallahan, Camilleri, Smith, & Bowyer, 1992).

Lactofen, a diphenyl ether, has an asymmetrically substituted C atom and comprises a pair of enantiomers; the herbicidal activity mostly comes from the *S*-(+)-enantiomer. This herbicide is applied as a foliar spray on target weeds and is used to control broadleaf weeds in soybeans, cereal crops, potatoes, and peanuts (Diao et al., 2009).

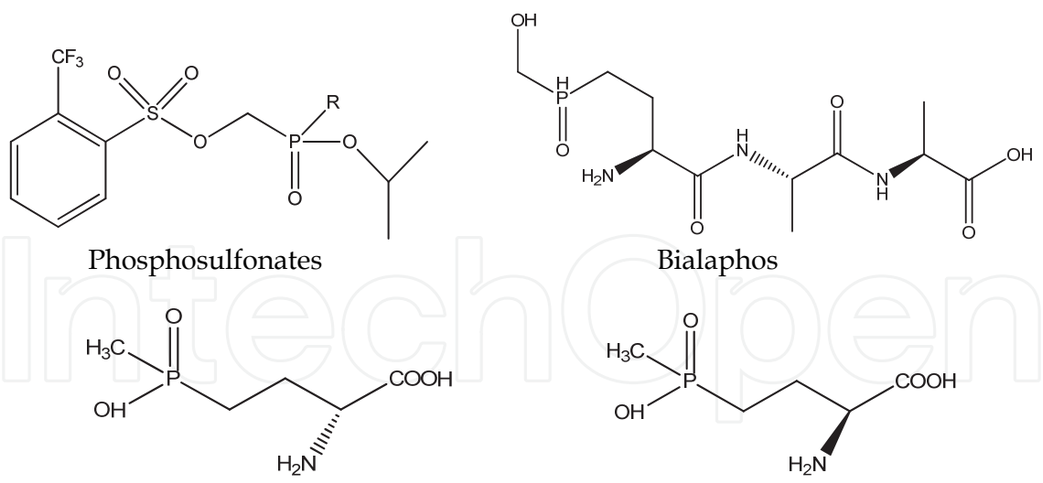


Diphenyl ethers Lactofen (2-ethoxy-1-methyl-2-oxoethyl-5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate)

Fig. 6. Chemical structures of diphenyl ethers.

2.6 Other chiral herbicides

Some organophosphorus compounds (Fig. 7) are used as herbicides. In *in vitro* activity studies, the active site of acetylcholine esterase (AChE) may interact differently with the different enantiomers of these compounds, but enantioselective differences in metabolic detoxification or toxicity may also be a major factor in determining the activity of organophosphorus herbicides.



Phosphosulfonates Bialaphos

D-Glufosinate L-Glufosinate

Fig. 7. Chemical structures of organophosphorus herbicides.

Phosphosulfonates are a class of soil-applied herbicides with activity against a variety of grassy weeds, and their chirality is attributed to an asymmetrically substituted phosphorus atom. Biological testing of the enantiomeric phosphosulfonate herbicides demonstrated that the purified (+)-enantiomer is more active than the racemate (Spangler et al., 1999). Bialaphos, another organophosphorus herbicide, has carbon chiral centres, and its *S*-(+)-

isomer is more active as a herbicide than its *R*-(-)-isomer. Glufosinate, also an organophosphorus herbicide, was used as its ammonium salt, and the activity of its enantiomers was studied using cell culture in several plant species. The results illustrated that the glufosinate racemate and L-glufosinte are transformed into the same metabolites, but D-glufosinate is not metabolized (Muller, Zumdick, Schuphan, & Schmidt, 2001; RuhlandEngelhardt & Pawlizki, 2002).

Certain triazines (Fig. 8) are often used as plant growth regulators. The ones having a chiral nitrogen center, such as amitrole, atrazine, cyanazine, and simazine, are effectively achiral because their enantiomers can easily be interconverted. The triazines with chiral C centres are used as selective weed killers and act by inhibiting photosynthesis (W. LiuJ. Ye & M. Jin, 2009).

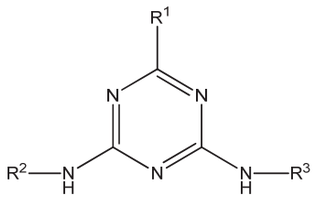
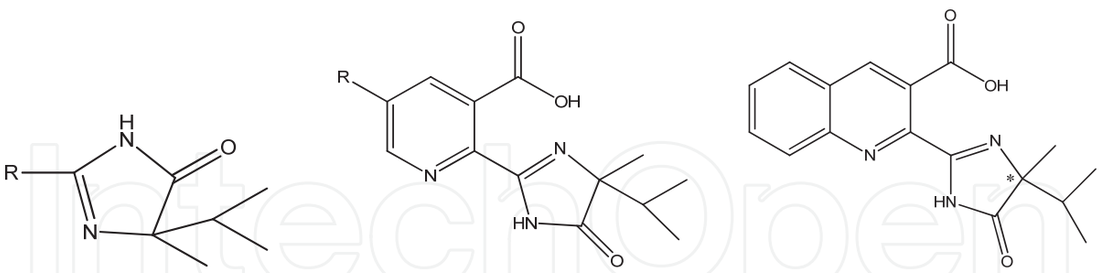


Fig. 8. Chemical structures of triazines.

All imidazolinone herbicides (Fig. 9) are chiral, and imazapyr, imazapic, imazethapyr, imazamox and imazaquin are widely used herbicides from the imidazolinone family (Lao & Gan, 2006). It has been reported that their *R*-enantiomers are 10 times more inhibitory toward the enzyme acetolactate synthase (ALS) than their *S*-enantiomers (Chin, Wong, Pont, & Karu, 2002). Imazethapyr (IM) is always absorbed through the roots of plants, and Zhou et al. found that *R*-(-)-IM affected the root growth of maize seedlings more severely than *S*-(+)-IM (Zhou, Xu, Zhang, & Liu, 2009).



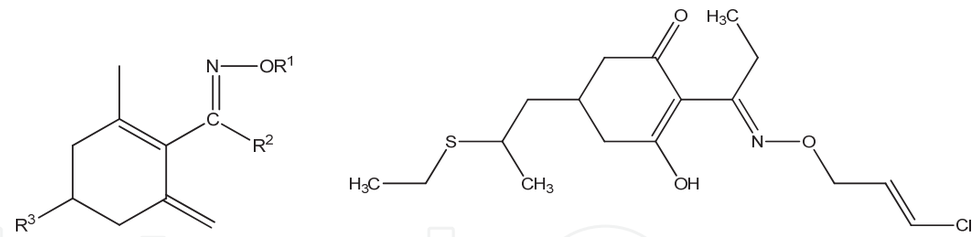
IM

Imazapyr: R=H; imazapic:R=CH_3;
imazethapyr:R=CH_2CH_3;
imazamox: R=CH_2OCH_3

Imazaquin

Fig. 9. Chemical structures of imidazolinone herbicides.

Cyclonenes (Fig. 10), which are used to control broadleaf weeds and can be absorbed by the leaves of plants, can inhibit the synthesis of fatty acids by acting on acetyl-CoA carboxylase. Among cyclonenes, clethodim is a selective post-emergence herbicide for the control of annual and perennial grasses. The optically pure (-)-enantiomer of clethodim was, surprisingly, more effective in regulating the growth of grass plants than the corresponding racemic mixture or the optically pure (+)-enantiomer (Whittington et al., 2001).



Cyclonenes clethodim

Fig. 10. Chemical structures of cyclonenes.

3. Enantioselective toxicity of chiral herbicides on non-target organisms

Different enantiomers of chiral herbicides can have different potencies on their target plants, and they also may have enantioselective toxic effects on non-target organisms. In previous studies, researchers always focused on the efficacy of chiral herbicides while neglecting the negative biological effects associated with particular enantiomers that might persist in the environment long after application. The potential biological toxicities of these herbicides, which could include chronic toxicity, acute toxicity and phytotoxicity, are generally enantioselective. When the Environmental Protection Agency (EPA) developed its assessment method for acute toxicity testing using *Daphnia* and *Ceriodaphnia dubia* as aquatic indicators, many researches around the world undertook studies of the enantioselective toxicity and molecular mechanisms of chiral herbicides using both *in vivo* and *in vitro* models. Lewis et al. found that all pasture samples from Brazilian soils preferentially transformed the non-herbicidal enantiomer of dichlorprop via a microbial transformation processes, whereas most forest sample transformed the herbicidal enantiomer more rapidly or as rapidly as the non-herbicidal enantiomer (Lewis et al., 1999). In general, the faster the microbial degradation processes remove the herbicides from the environment, the safer the effect of the herbicides is. Hence, using a pure enantiomer that is more active and safe than its partner or racemate is likely to cause less environmental damage and to pose less ecological risk (Hegeman & Laane, 2002).

3.1 Enantioselectivity in the chronic toxicity of chiral herbicides

For chiral pesticides, there have been several reports describing enantioselective chronic toxicity, but there are few such reports about herbicides. They are limited to a small number of reports about metolachlor. Zhan and Xu used silkworm as a biological indicator to investigate the enantioselective toxicity of metolachlor as estimated by the metabolism and activities of silkworm. Their researches mainly focused on enzyme activities, and the results suggested that rac-metolachlor and *S*-metolachlor have different effects on enzyme activities of fifth-instar silkworms (*Bombyx mori* L.). Acid phosphatase (ACP) activity in silkworm hemolymph was 44-73% higher in control organisms than in those treated with rac-metolachlor, but there was no great difference between *S*-metolachlor treatment and the control. Hemolymph lactate dehydrogenase and catalase activities were much lower in rac-metolachlor-treated silkworms than in *S*-metolachlor-treated ones. For midgut alkaline phosphatase activity, the activity found in controls was greater than in those treated with rac-enantiomers, which in turn was greater than the activity found in *S*-metolachlor-treated silkworms(Zhan, 2006). Changes in avoidance behaviour, body weight and *in vivo* enzyme

activity were found in earthworms (*Eisenia foetida*, *E.foetida*) studied by Xu et al. When the same treatment concentrations were used, the effects of rac-metolachlor on the enzyme activities and body weight of *E.foetida* were more significant than those of *S*-metolachlor. In 2 days and 7 days' experiments, the effects of the *S*-enantiomer on cellulase and catalase activities occurred more quickly, but over the long term (14 days, 28 days), the rac-enantiomer had greater toxic effects. The test of avoidance behaviour shows that earthworms are more sensitive to the stimulation of rac-metolachlor than that of *S*-metolachlor(Xu et al., 2010) . Those two studies indicate that the rac-metolachlor is more toxic to economically important silkworms than *S*-metolachlor, and they show that the metabolic inhibition is mediated by an inhibitory effect on enzyme activity.

In a chronic toxicity test of rac-metolachlor and *S*-metolachlor, the lowest-observed-effect concentration (LOEC), no-observed-effect concentration(NOEC), number of days to first brood, length, longevity, number of broods per female, number of young per female, and the intrinsic rate of natural increase were determined using *Daphnia magna* as an indicator. The LOEC and NOEC of the rac-enantiomers were much lower than those of the *S*-enantiomers, and the longevity and number of broods per female were significantly affected when the rac-enantiomer concentration was higher than 1.0 mg L^{-1} or when the *S*-enantiomer concentration was higher than 10 mg L^{-1}. Also, the number of broods per female and the intrinsic rate of natural increase were significantly reduced when the rac-enantiomers concentration was higher than 0.01 mg L^{-1} or the *S*-enantiomers concentration was higher than 0.5 mg L^{-1}. Body length was affected by both of the herbicides, but the number of days to first brood was not affected (Liu, Ye, Zhan, & Liu, 2006). These results were in agreement with the earthworm experiments described above and showed that the chronic toxicity of metolachlor is significantly higher than that of *S*-metolachlor.

3.2 Enantioselectivity in the acute toxicity of chiral herbicides

Early studies on the enantioselective toxicity of chiral pesticides primarily tested their acute toxicity in living organisms. Dramatic differences between enantiomers were observed in tests of acute toxicity toward terrestrial and freshwater invertebrates, suggesting that the acute toxicity is primarily attributable to a specific enantiomer in the racemates. In a study using *Chlorella pyrenoidosa* to test the acute toxicity of rac-metolachlor and *S*-metolachlor, the growth inhibition rate, chlorophyll *a* and chlorophyll *b* concentrations, catalase activity and ultrastructural morphology of cells were used as toxicity endpoints. The values of the 24, 48, 72, and 96 h EC_{50} and the chlorophyll *a* and chlorophyll *b* concentrations measured in the organisms exposed to rac-metolachlor were higher than those obtained when the *S*-enantiomer was used. The catalase activity of *C. pyrenoidosa* after treatment with *S*-metolachlor for 96 h was higher than after treatment with rac-metolachlor (Liu & Xiong, 2009). The acute 24-h LC_{50} of rac- and *S*-metolachlor were also assayed in *D. magna*, and the results showed that the rac-metolachlor LC_{50} was higher than that of the *S*-isomer (Liu et al., 2006). Both of these studies indicated that *S*-metolachlor was more toxic to aquatic organisms than rac-metolachlor. Another study of acute toxicity employed a standard OECD filter paper test, an artificial soil test and a natural soil test, and this study found that there were almost no enantioselective differences in the LC_{50} for earthworms, indicating that the acute toxicities of the two chiral herbicides displayed no enantioselectivity(Xu et al., 2009).

The dissipation and degradation of the herbicide lactofen are enantioselective processes: under laboratory conditions using enantioselective HPLC, the *S*-(+)-enantiomer is degraded faster than the *R*-(-)-enantiomer, producing residues enriched with *R*-(-)-lactofen when the racemic compound is incubated under aerobic and anaerobic conditions in sediments (Diao et al., 2009). The enantioselective acute toxicity of individual enantiomers of lactofen and its metabolite, desethyl lactofen, were studied in *D. magna*. The observed LC_{50} values of *S*-(+), rac-, and *R*-(-)-lactofen were 17.689, 4.308, and 0.378 μg/mL, respectively, and the corresponding values for desethyl lactofen showed a similar pattern (Diao et al., 2010). Therefore, the preferential degradation of *S*-(+)-lactofen leads to a higher concentration of the *R*-(-)-enantiomer, which has been shown to have higher acute toxicity to the non-target organism *D. magna*.

The acute toxicity of a series of organophosphorous compounds (OPs), 1-(substituted phenoxyacetoxy)alkylphosphonates (Fig. 11), which contain a chiral carbon atom, was also studied, and these compounds also display enantioselectivity. In an aquatic toxicity test using *D. magna* as an indicator, the *in vivo* assays showed that there is a significant difference in LC_{50} between the two enantiomers of *O*,*O*-dimethyl-1-(4-chlor- ophenoxyacetoxy) ethylphosphonate, with the (+)-enantiomer being 8.08 times more toxic than the (-)-form. Although the difference between the enantiomers of the other compounds in this study is not remarkable (1.2 to 4.2-fold), it can nevertheless be inferred that the toxicities of most chiral OPs are enantioselective (Li et al., 2008).

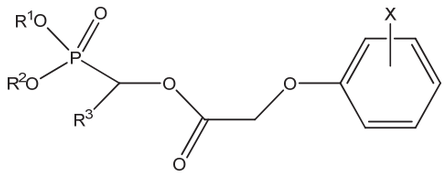


Fig. 11. Chemical structure of 1-(substituted phenoxyacetoxy)alkylphosphonates.

3.3 Enantioselectivity in the phytotoxicity of chiral herbicides

Many herbicides have been shown to be toxic to non-target plants, but our understanding of the enantioselective phytotoxicity of chiral herbicides is still limited. The chiral herbicide dichlorprop-methyl (2,4-DCPPM, Fig. 12) was clearly shown to have enantioselective toxicity toward *Chlorella pyrenoidosa*, *Chlorella vulgaris* and *Scenedesmus obliquus*. The rank order of enantiomer phytotoxicity was given by *R*-2,4-DCPPM > *S*-2,4-DCPPM > rac-2,4-DCPPM, and the toxicity of *R*-2,4-DCPPM was found to be about 8-fold higher than that of rac-2,4-DCPPM. All three algae species degraded 2,4-DCPPM quickly, but extraordinarily, rac-2,4-DCPPM was preferentially degraded by *Scenedesmus obliquus* at a much faster rate than the *S*- or *R*-enantiomers alone (racemate>*R*->*S*-), such that the racemate showed low toxicity compared to the other enantiomers. This phenomenon might occur because the *R*- and *S*-enantiomers are not hydrolyzed in the first 12 hours, and hydrolysis proceeds slowly after 12 hours (Li, Yuan, Shen, Wen, & Liu, 2008).

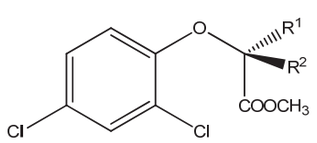


Fig. 12. Chemical structure of 2,4-DCPPM. R^1=H, R^2=CH_3 OR R^1=CH_3, R^2=H.

Several studies focused on the enantioselective phytotoxicity of IM, an herbicide widely used because of its low application rate, low toxicity to animals and broad spectrum of weed control activity (TanEvans & Singh, 2006). Zhou et al. evaluated the phytotoxicity of IM on the roots of maize (*Zea mays L.*) seedlings. Plant growth measurements and morphological, microscopic, and ultrastructural observations were conducted after treatment with individual IM enantiomers and the racemate. Although the different enantiomers showed the same trend of effects on indicators, *R*-(-)-IM affected the root growth of maize seeding more severely than *S*-(+)-IM (Zhou et al., 2009). Another study used seedlings of Xiushui 63, a Japonica rice variety to evaluate the phytotoxicity of IM; in this study, rice seedling morphology, antioxidant enzyme activity, oxidation markers and gene transcription were used as endpoints. Different enantiomers of IM also showed the same trend of effects on the seedling morphology of rice, but the levels of inhibition observed in roots and shoots showed enantioselectivity. The maximal root relative inhibition and shoot relative inhibition were ranked as follows: *R*-(-)-IM > racemate > *S*-(+)-IM. The activities of SOD, POD, and CAT and the MDA content in plants treated with R-(-)-IM were higher than those in plants treated with *S*-(+)-IM. In seed tissue and shoot tissue, it was observed that *R*-(-)-IM inhibited gene transcription and mRNA expression more strongly than *S*-(+)-IM (Qian et al., 2009). Both of these studies concluded that *R*-(-)-IM was more toxic than *S*-(+)-IM.

Diclofop acid (Fig. 13), produced by hydrolysis of diclofop methyl, is an herbicidal form of diclofop methyl. Significant differences were observed between its two enantiomers in an acute toxicity (72 h EC_{50}) test using rice *Xiushui* 63 seedlings. The *S*-enantiomer showed stronger toxicity to leaves, and the *R*-enantiomer was found to be more toxic to roots. The Hill reaction activity test indicated that the two enantiomers had enantioselective effects on chloroplasts, but the effects were quite complex and needed further interpretation (Ye, Zhang, Zhang, Wen, & Liu, 2009). The herbicidally inactive *S*-(-)-enantiomers of both diclofop-methyl and diclofop have similar or higher toxicity than the *R*-(+) forms to algae, depending on the algal species used. Cai et al. showed that both rac-diclofop and *R*-diclofop decrease algal cell permeability and that the *R*-enantiomer shows stronger inhibition. In contrast, the *S*-enantiomer increases algal cell permeability when low treatment concentrations are used, and it reduces algal cell permeability to at lesser extent only at higher concentrations compared to the *R*-enantiomer and rac-diclofop. The enantioselective degradation of diclofop in algae cultures is controlled by the facilitated uptake by algae, whereas the enantioselective toxicity is primarily governed by passive uptake (CaiLiu & Sheng, 2008).

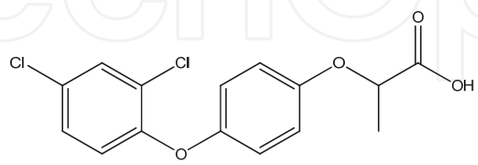


Fig. 13. Chemical structure of diclofop acid (*R*,*S*-2-[4-(2,4-dichlorophenoxy) phenoxy] propanoic acid)

4. Causative mechanisms of enantioselective herbicidal effects

The enantiomers of a chiral herbicide possess different biological activities, and one of the enantiomers usually shows a higher level of activity or toxicity. The enantiomers can alter

the activities and conformations of enzymes, thereby influencing their functions and metabolic effects. Therefore, the exploration of the causative mechanisms of enantioselective effects is regarded as one of primary goals of biological chemistry. Different receptors are enantioselectively affected by herbicides for different mechanistic reasons. Wen et al. found that the enantioselective behaviours of chiral compounds might change during interactions with different chiral receptors that coexist in different biological environments. They used UV differential spectrophotometry and fluorescence spectrophotometry to study the enantioselective interactions between *Penicillium expansum* alkaline lipase and dichlorprop (DCPP) herbicide. The ranking of dichlorprop compound interaction strengths with lipase was as follows: *R*-enantiomer > rac-DCPP >*S*-enantiomer. The lipase-catalyzed kinetic experiments proved that a hydrophobic interaction seemed to play a dominant role in the interactions, and they showed that the *R*-enantiomer inhibits lipase more severely, possibly due to its stronger interaction with lipase (Wen, Yuan, Shen, Liu, & Liu, 2009). To further study this interaction, the authors conducted several tests to evaluate the toxicities toward green algae of DCPP compounds and their complexes with chitosan molecules (DCPP-CS) and chitosan nanoparticles (DCPP-NP). The results showed that, without other chiral molecules, *S*-DCPP was more toxic to *Chlorella vulgaris* than *R*-DCPP, whereas to *Scenedesmus obliquus* and *Chlorella pyrenoidosa, R*-DCPP was more toxic. While in the presence of CS or NP, the chiral selectivity of DCPP could be changed. For instance, the order of inhibition to *Chlorella vulgaris* was as follows: *R*-DCPP-CS > *S*-DCPP-CS and *R*-DCPP-NP > *S*-DCPP-NP. This order was the complete opposite of that observed for *Scenedesmus obliquus* and *Chlorella pyrenoidosa* (Wen, Chen, Yuan, Xu, & Kang, 2011; Wen et al., 2010). Fluorescence spectroscopic analysis showed that the interaction between CS and DCPP enantiomers depends greatly on the steric structure of DCPP. A highly stereospecific interaction between herbicide and enzyme is thought to be the typical mechanism of enantioselectivity for chiral herbicides. The three-point model proposed by Easson and Stedman indicates that, when three ligands of an herbicide match three chiral locations in the active part of an enzyme, the herbicide will show maximum potency (Easson & Stedman, 1933). If the binding sites on the protein are in a cleft or on protruding residues, the four-location model developed by Mesecar should be considered (Zhou, Liu, Zhang, & Liu, 2007). For instance, IM is an ALS-inhibiting chiral herbicide. Qian et al. investigated the enantioselectivity of *R*- and *S*-IM in *Arabidopsis thaliana*. The result showed *R*-IM powerfully induced reactive oxygen species (ROS) formation while drastically reducing antioxidant gene transcription and enzyme activity, resulting in oxidative stress. This led to the accumulation of glucose, maltose and sucrose in the cytoplasm and chloroplast, and it disrupted the carbohydrate metabolism. This result proved that enantioselectivity also affects starch metabolism in *Arabidopsis thaliana* (Qian et al., 2011).

5. Further research opportunities

The activity and toxicity of chiral herbicides should be investigated at the chiral level because enantiomers of herbicides are known to selectively interact with biological molecules that are usually enantioselective and may behave as drastically different compounds. This enantioselectivitiy varies depending on the species of biological receptor; one enantiomer of an herbicide may inhibit the growth of a particular plant while stimulating the growth of other plants. A particular enantiomer of an herbicide may be more effective than the racemate, such that using enantiopure herbicides could increase their

potency for weeding and reduce the environmental burden applied chemicals. Techniques for separating the enantiomers of certain herbicides, such as chiral HPLC, GC columns (PirkleLee & Welch, 1997) and chiral electrophoresis(Desiderio, et al., 1997) , have been reported, but for economic reasons, many chiral herbicides with enantioselective activity are still used as racemic mixtures. It is important to find low-cost methods for separating the enantiomers of herbicides, which may require finding more effective chemical or biological catalysts for synthesising enantiopure herbicides.

Many previous studies have shown that, for some chiral herbicides, the active enantiomer may be environmentally degraded faster than the inactive enantiomer or the racemate, and the inactive enantiomer may even have stronger toxicity to non-target organisms. Thus, the abundance and high toxicity of the inactive enantiomer may produce passive effects in the environment. Considering the herbicidal enantioselectivity of degradation or toxicity alone would have limited environmental significance. It is important to consider both the degradation and toxicity of an herbicide enantiomer when predicting the environmental effects of the herbicide.

Herbicide activity at certain sites in non-target organisms has been reported. For instance, quizalofop and haloxyfop may inhibit ACCase, disrupt lipid metabolism and interfere with membrane transport. The potential enantioselective effects of chiral herbicides in these processes remain poorly understood and should be further explored. Though the activities and toxicities of many kinds of isolated enantiomers have been tested and reported, our understanding of the conversions between different enantiomers *in vivo* are still limited. One enantiomer may exhibit certain effects on biological receptors, but it may have opposite effects on the same target receptor when it changes into another enantiomer or racemate *in vivo*. Elucidating the transformation mechanisms and processes is a significant goal for further research. It seems that there is still a severe lack of knowledge about the characteristics and metabolism of chiral herbicides.

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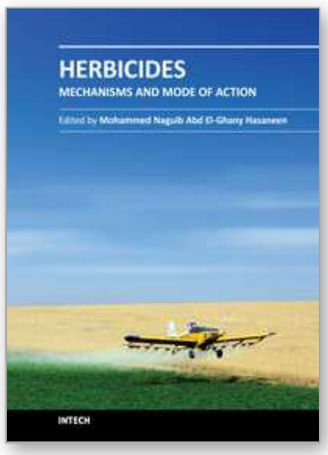

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This volume contains two sections: Mechanisms of herbicidal action (chapters 1-4) and Mode of action of selected herbicides on controlling diseased, weed growth and productivity and/or growth and development of field crops (chapters 5-10). Topics by chapters are: molecular mechanism of action, immunosensors , laboratory studies, molecular modeling, weed resistance, community response, use of herbicides in biotech culture, gene flow, herbicides and risk, herbicides persistence. These recurring themes reinforce my view, held over a very long time, that experience with one crop or problem can sometimes be relevant, often to an unexpected extent, to an apparently dissimilar situation in a different crop. I hope that readers interested in herbicides and pesticides will be satisfied with all the chapters in the book as its content might be of interest and value to them in the future.

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