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Review

Chiral pesticides

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The enantiomers of chiral pesticides are often metabolized at different rates. In agriculture, the preferred chiral form of a pesticide is more effective at lower application rates or more specific toward a targeted pest. Other advantages of chiral pure pesticides include greater environmental safety, reduced cost, greater specificity and extended patent life. Recent progress in optical resolution, asymmetric synthesis and biocatalysis of chiral pesticides has been described. Techniques to separate enantiomers with chiral HPLC and GC columns, electrophoresis and mass spectrometry have been reported. Chiral chase is actively pursuing asymmetric hydrogenation for the manufacture of a pure single-enantiomer pesticide. Enantioselectivity occurs in pesticidal activities toward target organisms as well as non-targeted organisms. There is a need to characterize both enantiomers of chiral pesticides in order to have an accurate understanding of their distribution and fate in the environment. Enantiomeric analysis can be useful in this aim and this is an important consideration in the risk assessment of pesticides. Use of only the target-active enantiomer of pesticides should be encouraged as it will reduce the pollutant load, provided it has no adverse impact on non-target organisms.

Keywords: chiral pesticides, enantioselectivity, chiral separation, chiral technology, toxicity.

Introduction

The agrochemical industry is continuously probing for new active compounds to control pests. The main aim of this research is therefore to develop new substances with lower application rates, increased selectivity and decreased undesired ecological impact. Many agrochemicals are chiral and each enantiomer may have different properties and effectiveness. Chiral pesticides are asymmetric and occur as isomers with two (or more) identical but non-superimposable mirror-image structures (enantiomers). The enantiomers of the chiral herbicide dichlorprop are shown in Fig. 1. Many pesticides consist of mixtures of stereoisomers, often with widely differing biological activities.[1)]

Generally, individual enantiomers of pesticides or their metabolites are not commercially available; however, the ability to separate enantiomers and produce a single enantiomeric isomer is gaining importance with pesticide manufacturers. Most chiral pesticides are used as racemates despite the fact that pesticidal activity is generally due to just one enantiomer while the other may have toxic effects on non-target organisms and thus the use of racemates contributes to unnecessary environmental loading.[2)]

About 30% of currently registered pesticide active ingredients contain one or more chiral centers.[3–5)] The production and use of target-active single- or enriched-enantiomer pesticides have provided green chemistry opportunities.[6)] Pesticides with chiral structures include pyrethroid insecticides, organochlorine pesticides, organophosphorus insecticides and fungicides, triazoles fungicides, acylanilides, aryloxypropanoates herbicides. Some examples of chiral pesticides bearing chiral atoms *e.g.*, carbon (metalaxyl **1**), phosphorus (profenofos **2**), both nitrogen and carbon (metolachlor **3**), sulphur

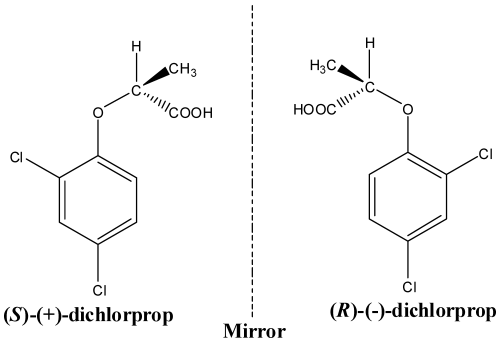

Fig. 1. Enantiomers of dichlorprop.

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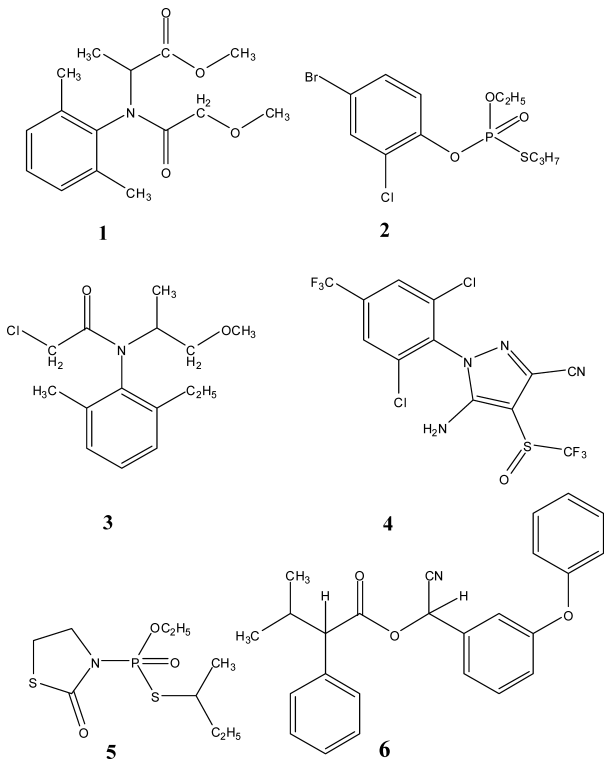


Fig. 2. Chemical structures of metalaxyl (**1**), profenofos (**2**), metolachlor (**3**), fipronil (**4**), fosthiazate (**5**) and fenvalerate (**6**) with different chiral atoms.

and nitrogen (fipronil **4**), both phosphorus and carbon (fosthiazate **5**), and both chiral carbons (fenvalerate **6**) are shown in Fig. 2.

Several pesticides currently on the market are either enantiopure *e.g.*, herbicides dichlorprop-P (**7**) (Fig. 3, structures **7**–**11**), fenoxaprop-P-ethyl (**8**), fungicide metalaxyl-M (**9**), insect growth regulator *S*-methoprene (**10**), enriched-enantiomer products such as *S*-metolachlor (**11**) or contain subsets of stereoisomers (*e.g.*, alpha-cypermethrin (**12**) (Fig. 4, structures **12**–**14**) (alpha-cypermethrin comprises two of the four *cis*-isomers out of total eight comprising cypermethrin), bioresmethrin (**13**), and deltamethrin (**14**).[7)]

Biological Significance of Chiral Isomers

A major development in pesticide research is the use of chiral chromatography and capillary electrophoresis to analyze individual chiral isomers.[8–11)] Chemically, chiral isomers are very similar, having the same boiling points, melting points, and typically the same solubility, reactivity, and other chemical properties. Microbially and biologically, however, they can behave very differently.[1)] The stereospecificity of chiral pesticides may be evident in activity at the desired biological target and/or at undesirable targets resulting in adverse effects as one form is active against the insects and pests that the pesticide is designed to attack, and the other form is inactive. In view of this, selective degradation is important for assessing pesticide risk to non-target organisms. Moreover, the switch

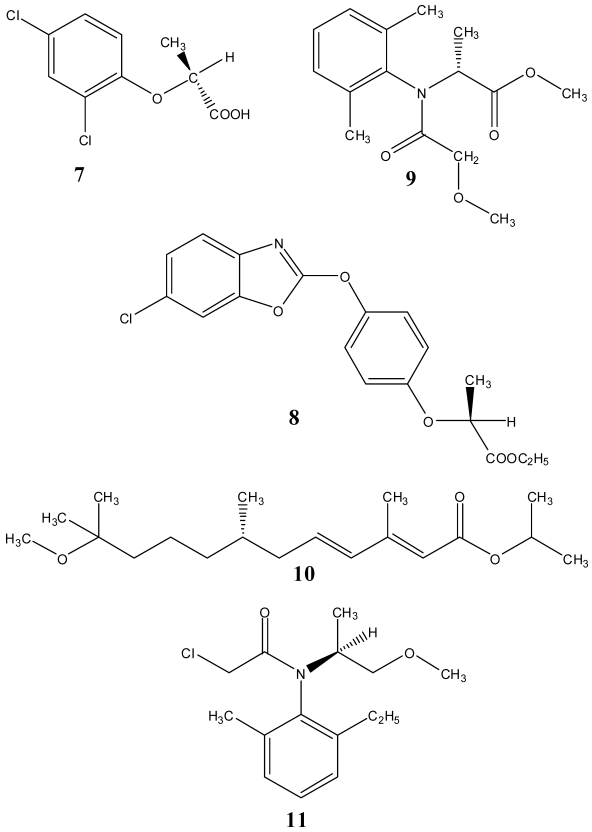


Fig. 3. Chemical structures of dichlorprop-P (**7**), fenoxaprop-P-ethyl (**8**), metalaxyl-M (**9**), *S*-methoprene (**10**) and *S*-metolachlor (**11**).

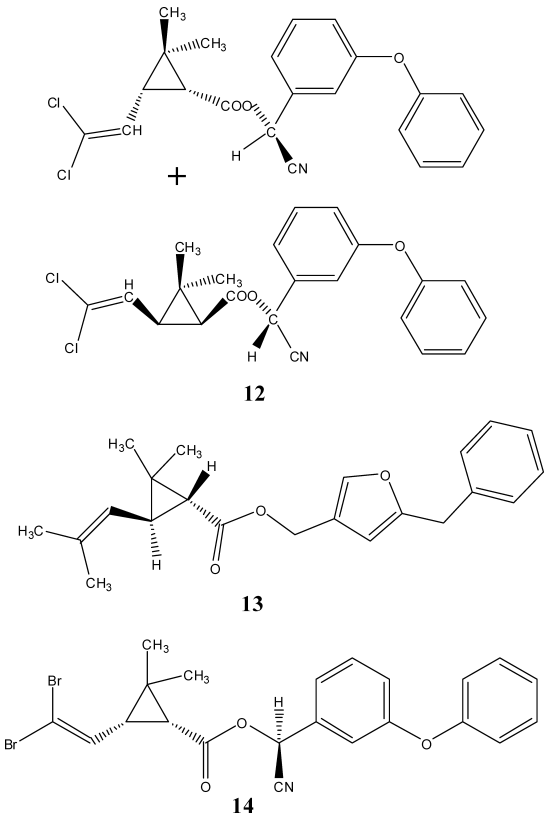


Fig. 4. Chemical structure of alpha-cypermethrin (**12**), bioresmethrin (**13**) and deltamethrin (**14**).

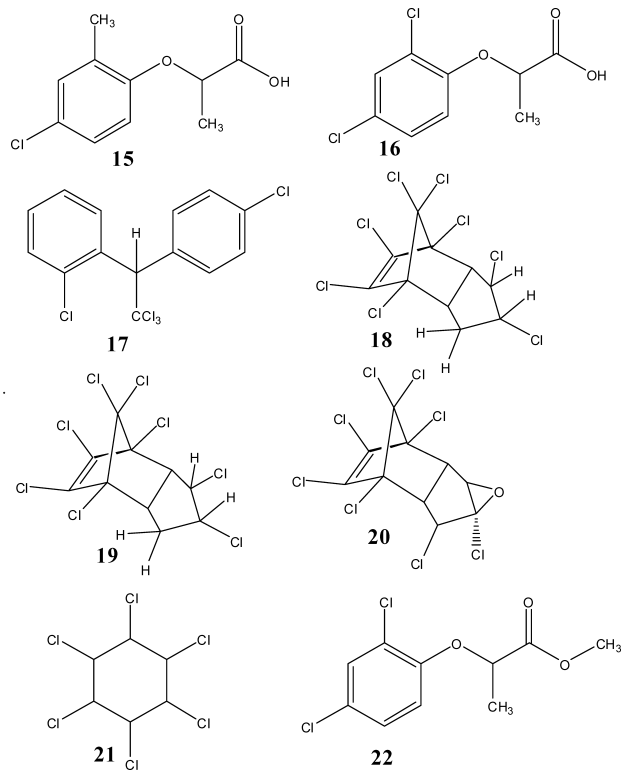


Fig. 5. Chemical structures of mecoprop (**15**), dichlorprop (**16**), *o,p′*-DDT (**17**), trans-chlordane (**18**), *cis*-chlordane (**19**), oxychlordane (**20**), hexachlorocyclohexane (**21**) and dichlorprop-methyl (**22**).

over to a single pure enantiomer pesticide is expected to result in lower environmental concentrations and in the changed enantiomer/stereoisomer composition of the residues.[12)]

Several European governments have required that mecoprop (**15**) (Fig. 5, structures **15**–**22**) and dichlorprop (**16**) be used as only their active *R* (+) enantiomers.[13)] All the fungicidal activity of metalaxyl (**1**) resides with the active (+)-enantiomer.[14)] and the degradation of metalaxyl (**1**) was shown to be enantioselective with the fungicidally active *R*-enantiomer being degraded faster than the inactive *S*-enantiomer, resulting in residues enriched with *S*-metalaxyl when the racemic compound was incubated.[15)] (+)-Enantiomer of fipronil (**4**), a phenylpyrazole broad-spectrum insecticide, was more toxic to *C. dubia* than the (−)-enantiomer[16)] but in other studies the (−)-enantiomer was shown to have significantly more androgen and progesterone activity than the (+) form.[3)] Enantioselective degradation occurred in human breast milk for *o,p′*-DDT (**17**), *trans*-chlordane (**18**), *cis*-chlordane (**19**), oxychlordane (**20**) and hexachlorocyclohexane (**21**) (Fig. 5), although pesticide levels were near or at detection limits for most compounds,[17)] however, changes in enantiomeric composition are still not well understood, and further investigation in this direction is recommended. Results on the toxicity and degradation of the herbicide dichlorprop-methyl (**22**) (Fig. 5) in algal cultures indicated that some physical and chemical properties of compounds are important in determining their enantioselective toxicity and degradation.[18)]

Chirality and Potential for Pesticide Reduction

Scientists are of the opinion that the production of pesticides using the active isomer has advantages which should be considered by industry in their research and development plans. By using pesticides with just the active isomer, farmers will likely achieve the same degree of pest control at a much-reduced dose of chemical use. Studies on chiral pesticides started to appear in the early 1990s.[19–28)] Companies have been deeply interested in selling synthetic chiral pesticides as single enantiomers in the past decade. The key reasons why single isomers are less common than they could be are probably limited access to chiral raw materials and economic synthetic routes. There is an increasing trend towards single enantiomers, not just because they perform in a superior manner to their racemic counterpart, but because of improved technology to obtain single enantiomers.

Enantiomeric Ratio and Enantiomer Fraction

Until recently, the enantiomeric ratio (ER) [ER=(+)-enantiomer/(−)-enantiomer] was the most frequently used descriptor of the relative abundance of environmental pollutants such as pesticides,[27)] however, the use of ER to indicate the relative

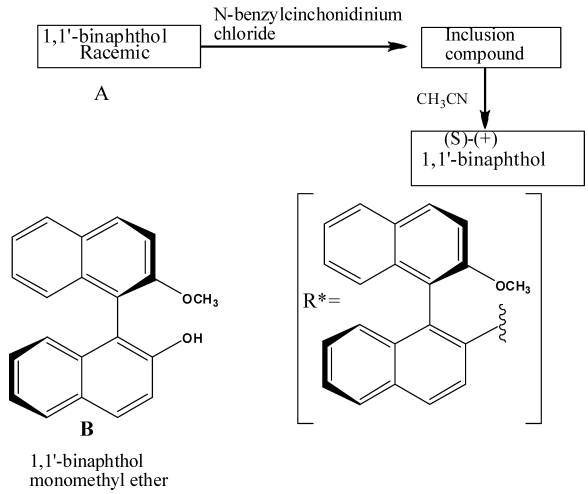
amounts of a pair of enantiomers in a sample has some disadvantages. ER can range from 0 to infinity and is equal to 1.00 for a racemic mixture, therefore, a unit change in ER away from unity in the downward direction (*i.e.*,<1) is not equivalent to the same unit change in the opposite direction. The enantiomeric fraction (EF) was proposed as a better reflector of chiral composition than conventional ER.[29] The EF can only range from 0 to 1.0 with EF=0.5 representing a racemic mixture. The relation between EF and ER can be expressed either as EF=ER/(ER+1) or EF=1/(1+1/ER). ER of chlordane-related compounds has been applied as an index of their environmental fates.[30] Experimental evidence of enantioselective microbial transformation of fipronil (**4**) in a natural environment (soil, water, and sediment) was reported and the EF of fipronil decreased from an initial racemic EF value of 0.46 to a value of 0.22 during the incubation period of active fipronil transformation, indicating preferential transformation of the *S*-(+)-enantiomer.[31]

Chiral Technology

The area of chiral technology is responsible for exciting new breakthroughs that have immensely impacted the discovery routes and the means of producing agrochemicals. A rising demand in agrochemical industries is to develop and sell chiral forms of insecticides, pesticides, herbicides and fungicides in enantiomerically pure form.[32] To meet this challenge, chemists have explored several approaches for acquiring enantiomerically pure compounds. These range from optical resolution and structural modification of naturally occurring chiral substances to asymmetric catalysis using synthetic chiral catalysts and enzymes.

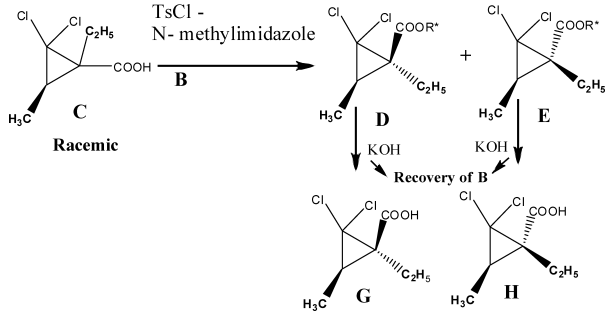
1. Optical resolution methods

The optical resolution method is widely used to obtain optically active compounds[33] and is an easy and practical method. One of the most common optical resolution methods utilizes diastereomers which are obtained from the reaction of racemic compounds and an optical resolving agent. The differences in physical properties between diastereomers are utilized in this method. Optical resolving agents are often easily obtained from natural products or synthesized,[34] for example, optical active 1,1′-binaphthol (BINOL) was obtained from *racemic* (BINOL) (A) by optical resolution.[35–38] (Scheme 1). In this method, the alkaloid *N*-benzylcinchonidinium chloride formed a crystalline inclusion compound. The inclusion compound of the *S*-enantiomer was found to be soluble in acetonitrile but that of the *R*-enantiomer was not. Optically active (BINOL) was also obtained from racemic BINOL by optical resolution employing HPLC with chiral stationary phases comprising 3,5-dinitrobenzoyl-L-leucine as the chiral selector, and the most important interactions for complexation were H-bonding accomplished through the hydroxyl protons of BINOL with carbonyl groups of 3,5-dinitrobenzoyl-L-leucine.[39]



Scheme 1. Optical resolution method for obtaining optical active 1, 1′-binaphthol (BINOL) from racemic (BINOL).

A series of monoalkyl ethers of optically active BINOL has been synthesized using the Mitsunobu reaction.[40] Chiral BINOL derivatives are well-recognized chiral catalysts and auxiliaries for the production of various useful optically active compounds[41] and numerous asymmetric reactions have been developed using chiral BINOL derivatives as chiral templates.[42] Researchers have reported the preparation of a precursor (substituted dichlorocyclopropanecarboxylic acid chloride, *R*-(+)-*p*-chlorophenethylamine) for the active substance carpropamid (**23**) (Fig. 6, structures **23**–**26**) as well as the reaction scheme for the preparation of carpropamid (**23**), individual stereoisomers of which were analyzed by HPLC using the chiral separation phase.[43] Scientists reported an efficient practical and systematic optical resolution method for gem-dihalocyclopropanecarboxylic acid (C) using chiral 1,1′-binaphthol monomethyl ether (B) as the key auxiliary to obtain (G) and (H) (Scheme 2).[41] Moreover, this method was applied to the synthesis of chiral pesticides [carpropamid (**23**), fencyclate (**24**) and pyrethroid with three asymmetric centers (**25**)[41]] (Fig. 6).



Scheme 2. Optical resolution method for gem-dihalocyclopropanecarboxylic acid (C) using chiral 1,1′-binaphthol monomethyl ether as the key auxiliary to obtain (G) and (H).

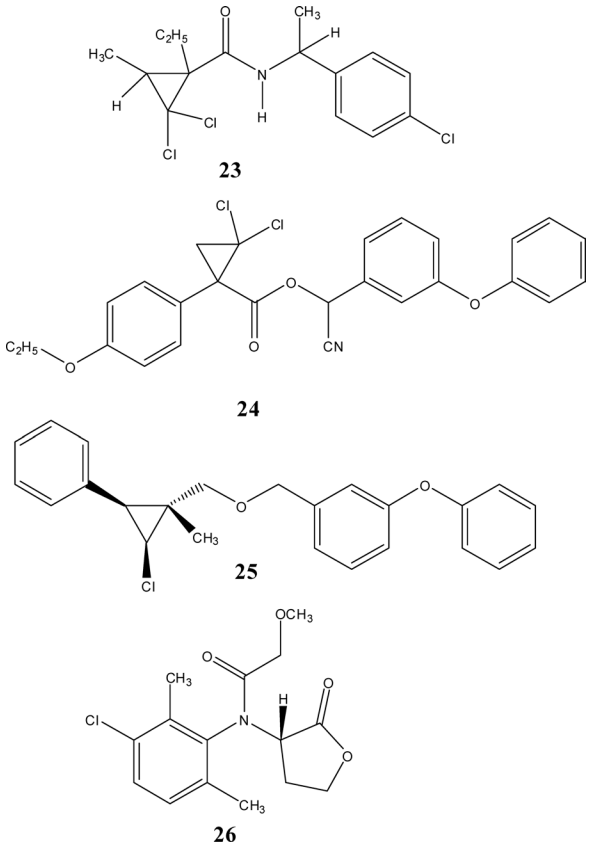


Fig. 6. Chemical structures of carpropamid (**23**), fencyclate (**24**), pyrethroid with three symmetric centers (**25**) and clozylacon (**26**).

Scientists reported BINOL derivatives suitable for use in the optical resolution of racemic amino acids or racemic amino alcohols or in the optical transformation of amino acids from D-form into L-form or *vice versa*.[44] Enantioselective protonation is a potent and efficient way to construct chiral carbons. Lewis acid-assisted chiral Bronsted acids (chiral LBAs) prepared from tin tetrachloride and optically active BINOL derivatives directly protonated various silyl enol ethers and ketene disilyl acetals to give the corresponding alpha-aryl or alpha-halo ketones and alpha-arylcarboxylic acids, respectively, with high enantiomeric excess (up to 98% ee). Further, a catalytic version of enantioselective protonation was also achieved using stoichiometric amounts of 2,6-dimethylphenol and catalytic amounts of monomethyl ether of optically active binaphthol in the presence of tin tetrachloride.[45] A novel chiral Sn(IV) aryloxide Lewis acid prepared from $SnCl_4$ and (*S*)-3,3′-bis[3,5-bis(trifluoromethyl) phenyl]-1,1′-bi-2-naphthol has been successfully applied to the enantioselective Diels–Alder reaction.[46] Among other methods, asymmetric catalysis is often the most efficient because a small amount of a chiral catalyst can be used to produce a large quantity of a chiral target molecule. Technical synthesis of the herbicides (*S*) enantiomer of metolachlor (**3**), (*R*) enantiomer of metalaxyl (**1**) and clozylacon (**26**) (Fig. 6) involved enantioselective hydrogenation of an imine intermediate using a novel iridium ferrocenyldiphosphine catalyst.[47]

2. *Chiral separations*

Monitoring the stereo-selective degradation and/or transformation of pesticide enantiomers is an important target in environmental chemistry. A review of chiral separation[48] provided details of the types of chiral phases used for separation and various separation techniques. Chiral selectors now include cyclodextrins, proteins, crown ethers, polysaccharides, polyacrylamides, polymeric chiral surfactants, macrocyclic antibiotics, and ergot alkaloids. Cyclodextrins (α, β, γ) remain the most popular chiral selectors for environmental applications.[49] Reviews on the enantiomeric enrichment of chiral pesticides in the environment,[27] chiral chromatography and on capillary electrophoresis[50–51] for chiral separation have been reported.

Chiral GC and HPLC methods appear to be complementary in the resolution of chiral pesticides, although certain pesticides can be resolved by both techniques.[52–55] It depends on the structure of the pesticide whether to choose the HPLC or GC method. Considering the attachment such as an aromatic ring, carboxyl, amine, hydroxyl, amide, carbonyl, alkoxyl or alkyl as functional groups, LC methods tend to work well with molecules having three or more such functional groups, and GC methods work well for compounds having fewer functional groups. Cyclodextrin-based GC chiral stationary phases such as G-TA (2,6-di-*O*-pentyl-3-trifluoroacetyl-γ-cyclodextrin), B-DM (2,3-di-*O*-methyl β-cyclodextrin) are the best choices for high to medium volatility pesticides. In the case of cyclodextrins, inclusion complex formation occurred, and a number of interactions such as pi–pi interactions, hydrogen bonding, dipole–dipole interactions, ionic bindings and steric effects controlled the formation of diastereomeric complexes.

Macrocyclic antibiotic-based HPLC chiral stationary phases such as macrocyclic glycopeptide (CHIROBIOTIC V and T) have been the most powerful tool in resolving a large variety of pesticides, on analytical and preparative scales alike.[52–55] Cyclodextrin (CYCLOBOND) chiral stationary phases also provided broad options in the resolution of chiral pesticides.[52–55] Capillary zone electrophoresis, micellar electrokinetic chromatography and electrochromatography have been used to develop separation methods for the resolution of herbicides enantiomers.[56–58] Recently, enantiomeric separation and quantification of various chiral pesticides by high-performance liquid chromatography and capillary electrophoresis have been reported by various researchers.[59–75] The general advantages of ICP-MS detection for chiral pesticide determinations in complex environmental samples have been reported.[76] Scientists determined the *S* and *R* isomers of metolachlor (**3**) in water by enantioselective enzyme immunoassay.[77] Separation of the two enantiomers of the organophosphorus pesticide ruelene (**27**) (Fig. 7, structures **27**–**29**) by capillary gas chromatography has been developed[72] A com-

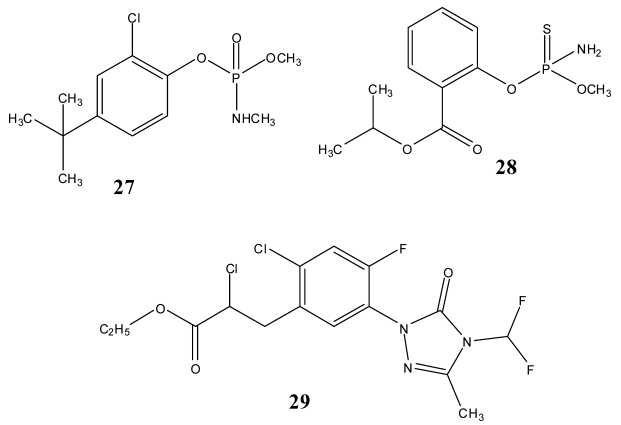


Fig. 7. Chemical structures of ruelene (**27**) isocarbophos (**28**) and carfentrazone-ethyl (**29**).

mercial pharmaceutical analysis chiral method development kit (Chirex Column Kit A, Phenomenex) was used to analyze six pesticide stereoisomer mixtures.[78)]

Chiral resolution study of pesticides showed that 2-propanol was more suitable for the chiral separation of isocarbophos (**28**) (Fig. 7) and carfentrazone-ethyl (**29**) (Fig. 7), and isobutanol was better for fipronil (**4**)[79)] and the resolution increased with the decreasing modifier content and temperature for all three chiral pesticides. Normal-phase high-performance liquid chromatography methods for the resolution of five chiral triazole pesticides, diniconazole (**30**) (Fig. 8, structures **30**–**34**), tebuconazole (**31**), hexaconazole (**32**), triadimefon

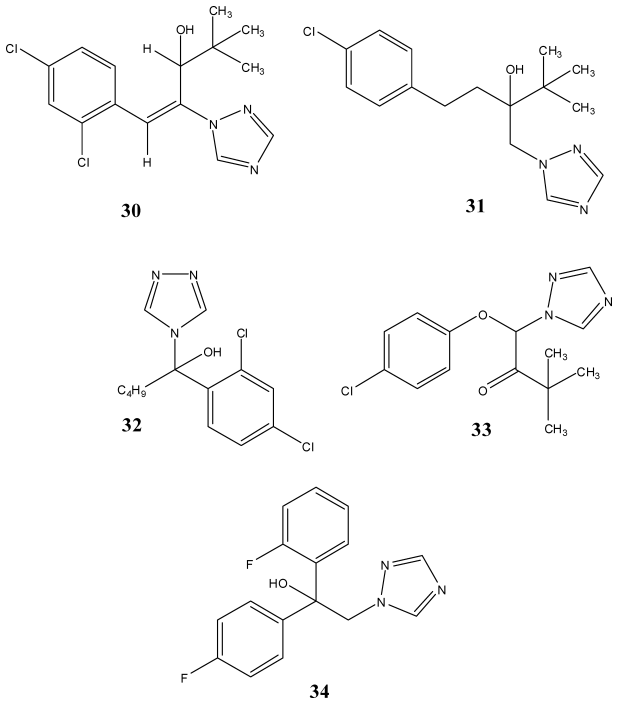


Fig. 8. Chemical structures of diniconazole (**30**), tebuconazole (**31**), hexaconazole (**32**), triadimefon (**33**) and flutriafol (**34**).

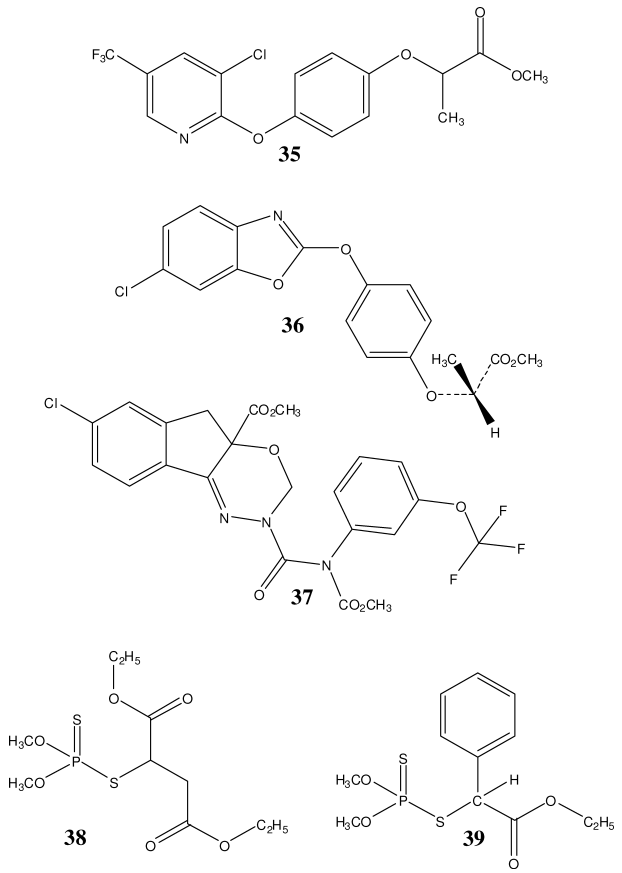


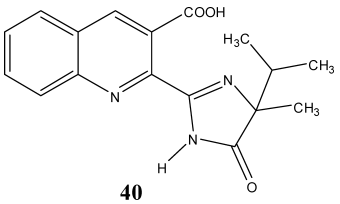
Fig. 9. Chemical structures of haloxyfop-methyl (**35**), fenoxaprop-*p*-ethyl (**36**), indoxacarb (**37**), malathion (**38**) and phenthoate (**39**).

(**33**) and flutriafol (**34**) (Fig. 8), in the chiral stationary phase were developed[73)] and better separation was achieved using 2% isobutanol for diniconazole (**30**), 2% ethanol for tebuconazole (**31**), 2% 2-propanol for hexaconazole (**32**), 1% 1-butanol for triadimefon (**33**) and 2% 1-propanol for flutriafol (**34**) as modifiers in *n*-hexane at 0°C with resolution factors of 1.62, 1.66, 2.46, 1.68 and 1.98, respectively. Chiral separation of three agrochemical toxins enantiomers by high-performance liquid chromatography in the vancomycin crystalline degradation product-chiral stationary phase showed excellent stereoselectivity for the two enantiomers of haloxyfop-methyl (**35**) (Fig. 9, structures **35**–**39**) and fenoxaprop-*p*-ethyl (**36**), and chiral recognition for indoxacarb (**37**) (Fig. 9) in normal-phase mode.[80)]

All four stereoisomers of fosthiazate (**5**), a chiral organophosphorus pesticide were separated with a Chiralpak (R) AD [amylase tris(3,5-dimethyl-phenyl carbamate)] column on high-performance liquid chromatography. Further, the stereoselective toxicity to *D. magna* found in fosthiazate suggested that the environmental safety of fosthiazate should be evaluated on the basis of its individual isomers.[81)] The separation of the enantiomers of malathion (**38**) and phenthoate (**39**) (Fig. 9) has been achieved by electrokinetic chromatography

using different anionic cyclodextrins as chiral selectors.[82] Normal-phase HPLC methods were employed for direct enantiomeric resolutions of chiral triazole pesticides by high-performance liquid chromatography.[83]

Capillary electrophoresis has high potential for the enantioseparation of agrochemicals in real samples.[75] Application of capillary electrophoresis has been shown to be a simple, efficient, and inexpensive way to study the enantioselective transformation of chiral pesticides.[84–85] The enantiomers of five chiral pesticides of environmental interest, metalaxyl (**1**), imazaquin (**40**) (Fig. 10, structures **40**–**43**)), fonofos (**41**), ruelene (**27**), and dichlorprop (**16**), were separated analytically using capillary electrophoresis with cyclodextrin chiral selectors.[84] Metalaxyl (**1**) was enantioseparated by capillary zone electrophoresis with γ-cyclodextrin as the chiral selector, and fonofos and imizaquin were enantioseparated using the micellar electrokinetic chromatography mode of capillary electrophoresis with γ-cyclodextrin and dimethyl-β-cyclodextrin respectively, as selectors.[84] Recently, a capillary electrophoresis separation method has been reported that has broad application for the separation and analysis of enantiomers of chiral pesticides [ruelene (**27**), a neutral organophosphorus insecticide, dichlorprop (**16**), an ionic phenoxyalkanoic acid herbicide, bromochloroacetic acid (**42**), Fig. 10] in a variety of environmental matrices such as enantioselective microbial transformation.[86] The method involved typical capillary electrophoresis techniques, with the addition of cyclodextrin chiral selectors to the electrolyte for enantiomer separation and also, in the case of ruelene (**27**), the further addition of a micelle-forming compound such as sodium dodecyl sulfate for separation using micellar electrokinetic chromatography mode of capillary electrophoresis. The procedure used an electrolyte containing 25 mM sodium tetraborate in deionized water of pH 8.5 with dilute HCl and containing 25 mM trimethy-β-cyclodextrins for dichlorprop; 50 mM sodium tetraborate in deionized water adjusted to pH 8.5 with dilute HCl and containing 40 mM trimethyl-β-cyclodextrins for bromochloroacetic acid; and 20 mM sodium tetraborate in deionized water of pH 8.5 using dilute HCl, containing 100 mM SDS, 20% acetonitrile, and 40 mM 2-hydroxypropyl-β-cyclodextrins for ruelene.[86] For CE analysis, the instrumental part of modern CE analysis is completely computer controlled and the parameter values selected through the computer were: temperature, 23°C; detector wavelength, 230 nm; voltage, 15 kV; injection type and time-hydrodynamic, usually for 5 sec; run time, 25 min for dichlorprop; and temperature, 23°C; detector wavelength, 200 nm; voltage, 25 kV; injection type and time- hydrodynamic, usually for 5 sec; run time, 25 min for bromochloroacetic acid; and temperature, 23°C; detector wavelength, 200 nm; voltage, 25 kV; injection type and time-hydrodynamic, usually for 5 sec; run time, 25 min for ruelene.[86] Ruelene enantiomers in a soil-water slurry at 50 mg/l of the ruelene racemate showed EF=0.50 at time zero and EF=0.40 at 100 days, while for bromochloroacetic acid EF=0.50 at zero time and EF=0.43 at 8 days[65] where [EF=area (+)-enantiomer/area of both enantiomers].[86]



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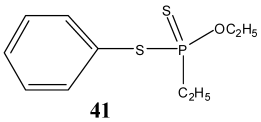

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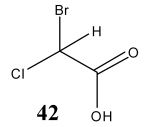

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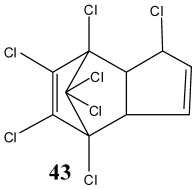

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Fig. 10. Chemical structures of imazaquin (**40**), fonofos (**41**), bromochloroacetic acid (**42**) and heptachlor (**43**).

To make more accurate risk assessments of chiral pesticides, it is necessary to understand the relative persistence and effects of their enantiomers. The toxicity of a pesticide or how long it persists in the environment depends on which mirror-image form of the chemical is present.[3] HPLC with circular dichroism detection can detect these pesticides and discriminate between +enantiomers.[87] Enantioselective metabolism of organochlorine pesticides in soil and water has shown that chiral pesticides change with the atmosphere.[88] Researchers found that one isomer of the fungicide metalaxyl (**1**) broke down more rapidly in acidic soils, while another isomer degraded more quickly when the pH of the soil rose above 5. They concluded that the soil and the presence of bacteria that breakdown chemicals are important factors in determining which isomer might become more prominent over time.[89] Based on the comparison of measured and calculated vibrational circular dichroism, the absolute configuration of (−)-enantiomer of heptachlor (**43**) (Fig. 10) can be assigned unambiguously as *1R*-heptachlor.[30] Preferential degradation of the *S*-(−) enantiomer of each chiral phenoxyalkanoic herbicide 2-(2,4-dichlorophenoxy)propionic acid (**16**) and 2-(4-chloro-2-methylphenoxy)propionic acid (**15**) herbicide was observed in most species of broad leaf weeds and soil, while degradation in all species of grass occurred without enantio-

selectivity.[90] Studies on the behavior of metalaxyl (**1**) and its pure *R*-enantiomer in sunflower plants (*Helianthus annus*) emphasized the importance of examining the fate of both stereoisomers of a chiral pesticide in an environmental system for the correct use of enantiomerically pure pesticides.[91]

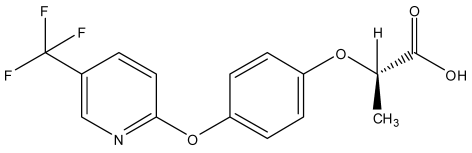
Chiral Synthons in Pesticide Synthesis

Important developments in the field have already been reviewed.[92] Chiral enabling technologies have essentially a 2-fold concern, *viz.*, chiral manufacturing which entails the production of pure enantiomers and chiral analysis which focuses on assay technologies to determine enantiomeric purity.[93] Practical technologies for the production of single enantiomer agrochemicals employ methods ranging from the extraction of natural products through to asymmetric synthesis and encompass physical, chemical and biological techniques.[94–95] Basic strategies to produce enantiomerically pure compounds include the use of naturally occurring optically active molecules as building blocks and asymmetric synthesis. Synthesis, absolute configuration, and analysis of malathion, malaoxon, and isomalathion enantiomers have been reported and malathion enantiomers prepared from (*R*)- or (*S*)-malic acid were converted to the corresponding enantiomers of malaoxon. The four isomalathion stereoisomers were prepared *via* two independent pathways using strychnine to resolve the asymmetric phosphorus moiety.[96–97]

Asymmetric synthesis is commonly used to prepare chiral compounds. The importance of chiral "synthons" in the preparation of new, structurally diverse, optically pure pesticides[98] as well as the application of enantioselective catalytic methods for the technical preparation of chiral pesticides [(*S*)-enantiomer of metolachlor (**3**), (*R*)-enantiomer of metalaxyl (**1**) and clozylacon (**26**)] has been reported.[99] The key step in the technical synthesis of the herbicide (*S*)-metolachlor (**11**) involved the enantioselective hydrogenation of an imine intermediate using a novel iridium ferrocenyl-diphosphine catalyst. Enantioselective hydrogenation of the corresponding enamides with Rh or Ru/binap catalysts was the key step in the synthesis of (*R*)-metalaxyl and clozylacon (**26**).

Researchers have integrated asymmetric synthesis and combinatorial chemistry to optimize the asymmetric synthetic process for the production of single versions of molecules producing substantially fewer toxic variants of organophosphorus pesticide with a phosphorus atom at the chiral centers.[100]

Biocatalysis is emerging as one of the greenest technologies. Chiral intermediates are in high demand by the agrochemical industry for the preparation of pure single enantiomer agricultural pesticides. Regulatory directives from government bodies are increasing the number of chiral molecules required by the agrochemical industry, where pure single-isomer pesticides seem to offer a lower dosage and reduced side effects. Biocatalysis is a rapidly developing area that uses micro-organisms and/or purified enzymes or enzyme



44

Fig. 11. Chemical structure of fluazifop-P (**44**).

analogues, nucleic acids, cells, or tissues to effect specific chemical transformations. Enzymatic reactions are now well recognized as an easy and dependable means of providing enantiomerically pure products.[101–103] Lipases are amongst the most important biocatalysts that carry out novel reactions in both aqueous and nonaqueous media and have remarkable ability to carry out a wide variety of chemo-, regio- and enantioselective transformations. The preparation and use of an enzyme (lipase) coated with an ionic liquid and its use as a catalyst for providing a chiral intermediate required in the synthesis of chiral pesticides has been reported.[104] Recently, the use of isolated enzymes and microorganisms as catalysts for the preparation of pesticides and their precursors has been reviewed.[105]

Scientists have established that lipase hydrolyzed binaphthol derivatives are connected with an appropriate linker. In this connection, an efficient linker-oriented design of 2,2′-binaphthol derivatives for optical resolution using *Candida antarctica* lipase B-catalyzed reaction was employed to prepare two types of optically active binaphthol derivatives, 1-[2-hydroxy-6-(naphthalen-1-yl)naphthalen-1-yl]-6-(naphthalen-1-yl)naphthalen-2-ol and 6-butyl-1-(6-butyl-2-hydroxynaphthalen-1-yl)naphthalen-2-ol.[106] Recently, the biocatalytic production of chiral alcohols utilizing isolated enzymes and whole cells has been reported.[107–108]

1. Biotechnology applications

Derivatives of chlorinated propionic acids are important building blocks in the synthesis of chiral agrochemicals such as dichlorprop (**16**) and fluazifop-P (**44**) (Fig. 11).[109] The potential exploitation of the properties of various dehalogenases in biotransformation will become economically attractive if microorganisms themselves or a crude preparation of them can be used as cheap catalysts.[110] Certain dehalogenases are highly stereospecific, for example, the 2HHA hydrolytic dehalogenase, which selectively dehalogenates D-isomeric substrates such as D-2MPCA. One commercial application of this property is the development of a novel herbicide using L-2MPCA as the starting material. The inexpensive racemic mixture of D, L-2MCPA only had half of the biological active material, so an initial treatment to remove unwanted D-2MCPA was developed.[111]

Chirality and Ecotoxicity

It is well agreed that the accumulation of substances to hazardous levels in living organisms poses environmental and

human health risks, which governments seek to reduce or eliminate. Environmental fate data are necessary to identify the stereoisomers and/or their transformation products to which non-target organisms might be actually exposed. Ecotoxicity data on separate isomers are necessary to fulfill the desired objectives of health and environment protection. Furthermore, it is important to know the toxicity of pesticide-active and pesticide-inactive stereoisomers to non-target organisms. Enantiomer exposure data have emerged over the past several years. Pesticide activity towards a target pest does not imply that the pesticide-active stereoisomer will be necessarily toxic to non-target organisms. Scientists are of the opinion that if adverse effects are caused only by or mostly by the excluded enantiomer, enantiomer-enriched products may offer great environmental benefits.[39] Moreover, this is known as a green chemistry measure. In this direction, the reduction of unfavorable toxicity to non-target organisms can be achieved by using a pure single enantiomer. Some supporting observations in the literature highlight this aspect.

This first survey on the role of chirality in ecotoxicological processes focuses on environmental trace analysis.[112] There was no significant difference in acute or residual activity between the racemic mixture and individual enantiomers of fipronil (**4**)[113], however, enantiomerically pure or enriched formulations of (−)-fipronil may reduce the impact on the nontarget organism *C. dubia*.[114–115] The most toxic isomer of (*S* +) and (*R* −) enantiomers of fipronil (**4**) has been found to be organism-specific.[116] Scientists have shown that compared with *S*-metolachlor, *rac*-metolachlor is more toxic to economically important silkworms[117] and to *D. magna*.[118] Results on the enantiomeric biotoxicity of the two enantiomers of chiral methamidophos (**45**) (Fig. 12) suggested that enantioselectivity and (−)-methamidophos (**45**) was found to be about 8.0–12.4 times more potent to acetylcholinesterases than its (+)-form based on *in vitro* assay, however, the (+)-enantiomer was 7 times more toxic to *D. magna* in 48 hr tests.[70]

Diclofop (**46**) and diclofop-methyl (**47**) (Fig. 12) belong to

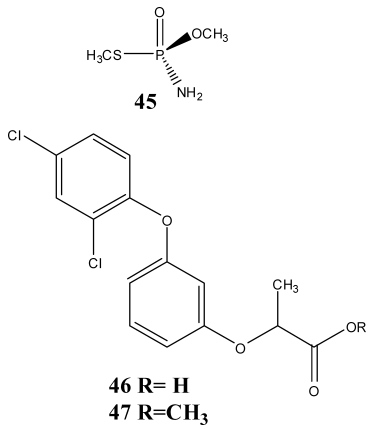


Fig. 12. Chemical structures of methamidophos (**45**), diclofop (**46**) and diclofop-methyl (**47**).

a class of chiral herbicides and only their *R* (+) form is herbicidally active. It has been reported that herbicidally inactive *S* (−) enantiomers of both were similar to or higher than the corresponding *R* (+) forms in toxicity to algae, depending on specific species.[119] In view of above, specific attention should thus be paid to racemic pesticides currently in use as less active or inactive enantiomers may pose higher ecological risks, however, according to a recent study, there is a need to conduct optical purity tests, in addition to a chemical purity test, for chiral pesticides.[120]

Conclusions and Perspectives

Certain enantiopure pesticides have been reported to be more effective than racemic mixtures, resulting in reduced quantities of chemicals being released into the environment. Use of the active isomer would reduce the chemical load without any loss of efficacy and remove some uncertainty from the risk assessment process; however, single enantiomer products may undergo chiral inversion or racemisation *in vivo*. The amount of racemization occurring *in vivo* must be quantified, since there would be no advantage in administering a single enantiomer compound on safety grounds if it was converted to the harmful enantiomer *in vivo*. At the same time, additional costs are involved in both the production and removal processes of non-active isomers. Techniques for the asymmetric synthesis and separation of enantiomers with chiral HPLC and GC columns, and chiral electrophoresis techniques have been developed for several pesticides. For strengthened research to improve preparation methods for pure enantio-pure isomers, there is scope to improve chemical catalysts for asymmetric hydrogenation. Scientists feel that in the near future at least, biocatalysis will continue to be most appropriate for synthesis in relatively narrow areas where chemical approaches are not desirable.

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