Chiral Pesticides: Identification, Description, and Environmental Implications

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Contents

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1 Introduction: Molecular Asymmetry in Pesticides

Anthropogenic chemicals, including pesticides, are a major source of contamination and pollution in the environment. Pesticides have many positive uses: increased food production, decreased damage to crops and structures, reduced disease vector populations, and more. Nevertheless, pesticide exposure can pose risks to humans and the environment, so various mitigation strategies make them safer, minimize their use, and reduce their unintended environment effects. One strategy that may help achieve these goals relies on the unique properties of chirality or molecular asymmetry. Some common terms related to chirality are defined in Table 1.

The likelihood of introducing new pesticides to the marketplace that contain multiple chiral centers and unresolved mixtures of stereoisomers has increased. The reason is because more natural products and their derivatives have become the source of inspiration for designing new pesticides, and the molecular structure of these compounds has become increasingly complex (Williams 1997). The trend toward more complex structures that have multiple chiral centers also has occurred in the pharmaceutical industry (Feher and Schmidt 2003). There is one major difference in how these chemicals are developed and produced: chiral drugs are routinely tested, and often intentionally marketed as individual stereoisomers, whereas pesticides generally are not (Williams 1996; Stanley and Brooks 2009).

If a single stereoisomeric form contains all of the desired pesticidal properties (i.e., the biologically active stereoisomer or eutomer), but an unresolved racemic (equal amounts) of the stereoisomers is applied, at least twice the amount of total chemical material is being applied than is necessary (Ariëns 1989). Specifically, if N chiral elements exist in the pesticide molecule, then there are 2^N maximum possible stereoisomers. If only one of the 2^N stereoisomers exhibits exclusive or dominant pesticidal activity, then the percent excess of minimally or inactive stereoisomers (distomers) in the applied material will be $(2^N–1) \div 2^N \times 100$, a 50% excess of distomer(s) for N= 1, a 75% excess for N= 2, etc. Although lacking intended pesticidal activity, any distomer(s) in the applied pesticide material may nevertheless have detrimental environmental consequences (e.g., to non-target organisms). Development and manufacturing processes that enrich the eutomer and minimize or eliminate the distomer(s) in formulated pesticides may, therefore, reduce chemical contamination, thus representing a more sustainable approach with ecosystems and environmental benefits.

Careful consideration of molecular structure is also important for scientists conducting pesticide environmental fate and effect studies, because substantial differences exist in the biological activity of distinct stereoisomers and their mixtures. Stereoisomers can degrade at different rates in the environment and in organisms, primarily through biological processes (Müller and Kohler 2004). Selective degradation of stereoisomers can alter risk factors because it potentially produces differences in exposure, toxicity and bioavailability. Fundamental to any research conducted on stereoisomers is the need to apply stereospecific analytical methods, especially chiral separation techniques, to characterize the asymmetric pesticide components that may exist in environmental and exposure studies. If non-chiral chemical analysis techniques are used in environmental or toxicological assessments, the unique properties of individual

stereoisomers in pesticide material are completely missed (Müller and Buser 1997). Many researchers have long treated isomers as discrete compounds that have unique properties; yet to this day, stereoisomers often are neglected in this regard.

This paper is intended for use by hands-on researchers such as chemists, toxicologists, environmental scientists, and modelers who wish to study the stereoisomers of environmental contaminants, particularly chiral pesticides. To assist researchers who are new to the application of chiral properties and principles, we address common stereochemical elements, provide identification of chiral pesticides, and indicate which have had potential enantioselective analysis techniques already developed for them. With this knowledge, we hope that more researchers will incorporate stereoisomer considerations into their repertoire. Furthermore, in this review, we list all known chiral pesticides in tabular and graphical formats and provide information on known enantioselective separation methodologies.

2 Methodology: Chiral Pesticide Dataset Curation

A list of pesticide active ingredients was compiled from two primary sources: the Pesticide Manual (electronic version 4.0/paper version 14) published by the British Crop Protection Council (Mann 2006), and the Compendium of Pesticide Common Names website (http://www.alanwood.net/pesticides/) maintained by Alan Wood (Wood 1995–2010). The Pesticide Manual contained 1,524 main and superseded product entries, which included chemicals and biological active ingredients used for the control of pests for crops, animals, and public health. The Compendium website contained 1,867 chemical entries and is updated several times a year. The cutoff date for entries on our list was December 2008. The pesticides listed in

these two references were reduced to 1,693 by eliminating duplications, grouping multiple names for the same compound, and grouping salts and esters with the parent compound.

If the two primary source references had identical chemical structure(s) for a given pesticide, the structure(s) were drawn using ChemBioDraw (CambridgeSoft 1986–2007) or ChemSketch (Advanced Chemistry Development 1994–2010). Additional internet sources, such as CambridgeSoft's ChemBioFinder website [http://www.chemfinder.com/; (CambridgeSoft 2010)] were consulted until a majority consensus was reached. The structures were saved as .cdx and .tif files. Assessment of molecular chirality was made, first by the authors observing the structure, who specifically looked for chirality elements such as axis, centers, and planes as defined by the International Union of Pure and Applied Chemistry (IUPAC 2006). Second, this determination was confirmed by computer software. In brief, the simplified molecular input line entry specification (SMILES) codes for all of the chiral pesticides were imported into Molecular Operating Environment [MOE; (Chemical Computing Group 2010)]. The "chiral" descriptor was used to output the number of stereogenic centers detected for each molecule entered in MOE database view. This algorithm does not tend to identify atropisomerism or heteroatomic stereogenic centers (such as chiral P or S). Discrepancies between the author's observation and computer software method were resolved by agreement among the authors. Fig. 1A shows a general schematic of the processes used for the construction and chemical structure analysis.

The chiral pesticides were grouped by primary use type: fungicide, herbicide, insecticide, or miscellaneous. This grouping is also used for discussion in the text, tables and figures. Chiral structures were compared with structures from the ChemSpider website, a free source of structure-based chemistry information [http://www.chemspider.com/; (Royal Society of Chemistry 2008)] for quality control purposes. Each chiral structure was scrutinized to identify

meso-compounds and constrained chiral centers (see Section 3 for further explanation). The indications of chirality: *, †, and curved arrows were added manually to each compound, based on visual inspection of the molecule (see Section 3). Fig. 1B shows a schematic of the processes used for each chiral pesticide.

ChirBase is the largest repository of enantioselective chromatographic separations. Three ChirBase databases, LC, GC, and CE [liquid and gas chromatography, capillary electrophoresis; (Koppenhoefer et al. 1993; Koppenhoefer et al. 1994; Advanced Chemistry Development 1997–2010)] were searched for each chiral pesticide name. ChirBase does not contain records for every published separation; however it is the most logical place to search for an extensive list of compounds. Any record that contained the pesticide name was considered a possible method. Evaluation of the records for duplication, and success of the separation method were not undertaken during this review. The methods resident in ChirBase generally are published in the literature and likely are replicable with the information provided.

3 Stereochemistry, Structures, and Names

Science involving the geometry and symmetry of molecules is a complex subject, and is beyond the scope of this review, although it is in the reader's best interest to become familiar with the Cahn-Ingold-Prelog rules for stereochemical notation (Cahn et al. 1966). Interested readers are directed to organic chemistry textbooks and writings for a comprehensive discussion of the subject (Mislow 1965; Nasipuri 1991; Eliel et al. 1994).

Briefly, a chiral center (or stereogenic center, or center of molecular asymmetry) occurs when four unique functional groups are bonded to an sp^3 hybridized center (i.e., with a tetrahedral geometry), which usually results in an asymmetric (chiral) molecule (Nasipuri 1991;

IUPAC 2006). This geometric configuration occurs most commonly when the chiral center is a carbon atom, and results in non-superimposable mirror-image stereoisomers that are referred to as enantiomers (see Fig. 2A). A lone pair of electrons on an atom in the second or higher row of the periodic table (S, P, As, etc.) can act as a fourth functional group (see Fig. 2B), and produce a non-carbon chiral center that similarly is configurationally stable and produces enantiomers (Nasipuri 1991). In this review, chiral centers are identified with an asterisk (*) in the figures.

Hindered rotation about a bond can result in a unique form of molecular asymmetry known as dissymmetry (or atropisomerism or axial chirality) in which no specific chiral center gives rise to asymmetry, but rather the molecule as a whole is chiral (Nasipuri 1991; IUPAC 2006). These conditions result in stereoisomers that are also non-superimposable mirror images, and, thus consitute a pair of enantiomers (Eliel et al. 1994). Atropisomers that are reportedly stable at room temperature are identified in the figures with a curved arrow at the hindered bond (see Fig. 2C). Another type of chirality arises from the lack of a plane or point of symmetry within the molecule (see Fig. 2D). This type of chirality is prevalent in cyclic compounds and is noted in the figures by a dagger (†). Some pesticides have multiple chiral centers (N) and produce a theoretical maximum of 4, 8, 16 or even more different stereoisomers (2^N).

Some specific molecules that contain multiple chiral centers and diastereoisomers (stereoisomers not related as enantiomers) will have less than 2^N stereoisomers, because they contain superimposable meso-compounds (see Fig. 2E) (IUPAC 2006). This situation often arises as a result of a symmetric structure with the two halves of the molecule having opposite configuration (Wade 1991). Pesticides that have meso-structures will be identified as such in the tables. Structures containing chiral centers at the junction of fused ring systems (see Fig. 2F) often have constrained geometries, resulting in intolerable bond angles and unstable

configurations (Mislow 1965). Pesticides that have constrained chiral centers will be identified as such in the tables. Both meso-compounds and constrained geometries will reduce the total number of stereoisomers possible to less than the 2^N theoretical maximum.

Pesticide structures in the figures are drawn in a generic, non-specific format, because multiple isomers (not due to chirality) exist for some compounds (e.g., *cis*/*trans*-isomers for the pyrethroid insecticides). When a pesticide contains multiple compounds, all structures are shown for completeness, regardless of whether they are chiral or not. When the main component of a pesticide is achiral (e.g., *p,p'*-DDT), but an isomer is chiral (e.g., *o,p'*-DDT), the main, most recognizable name and structure are used, with a note added about the chiral form for explanation.

Wherever possible, we have used the International Organization for Standardization (ISO) or other approved, recommended common or trivial names of pesticides in this review to promote easy recognition and brevity. Some additional names and abbreviations also are provided in the tables; however, trade names typically are not included. Pesticide development codes are provided for several pesticides for which a common name has only recently been, or is not yet, established. Both the figures and tables have been alphabetized using a Microsoft sort, which places numbers before letters.

All Chemical Abstract Service (CAS) registry numbers found related to a given compound have been included. This may reflect unique CAS numbers for different formulations (technical mixtures), isomers (*cis*/*trans*), salts, esters, stereochemistries, or for other reasons. Because CAS numbers are provided, official CAS registry names generally are not included in this review.

4 Identification and Discussion

4.1 Fungicides

In Table 2, we list 97 chiral fungicides, and show their structures in Fig. 3. In general, these fungicides have one to four chiral centers. The antibiotic subgroup of fungicides (aureofungin, blasticidin-S, cycloheximide, griseofulvin, kasugamycin, natamycin, polyoxin, and validamycin) has very complex structures that typically are prepared using semisynthetic strategies. These strategies use some starting materials that have defined absolute stereochemistry, reducing the number of possible stereoisomeric permutations, —a nice feature, because these complex structures contain numerous chiral centers. Although the structure for aureofungin was not located during our searches, it is undoubtedly chiral and was included because it contains more than 50 carbon atoms and has a close relationship to other chiral antibiotic fungicides. Dehydroacetic acid can undergo keto-enol tautomerization; whereas the keto form is usually favored, the equilibrium for this compound may lie with an achiral tautomer. ESBP (common name for O-Ethyl S-Benzyl Phenylphosphonothioate), fosetyl, and hexylthiofos each have a chiral phosphorus atom, and thicyofen has a chiral sulfur atom. Sulfur has a lone pair of electrons that can act as a fourth "group," which, combined with three other unique functional groups, creates a chiral center. Heteroatomic stereogenic centers (i.e., chiral S, P, etc., but not C) tend not to be encoded frequently in stereoisomeric identification codes, such as the one used from MOE (Chemical Computing Group 2010), because these moieties are more commonly encountered in agrochemical functionalities than in drug design.

In Fig. 3, all possible chiral centers have been marked, but restrictions in ring configurations (e.g., fused rings; see Fig. 2F) may yield fewer stereoisomers. Compounds that have such constraints include captafol, captan, gliotoxin, isopyrazam and procymidone.

Constrained chiral centers are enumerated in Table 2, along with the existence of meso forms for 9 fungicides. Ring constraints and meso forms will need to be considered for calculating the number of possible forms prior to undertaking the analysis of stereoisomers.

There are additional reasons for compounds having less than the maximum number of stereoisomers, and these must be recognized and understood prior to analysis. Because the antibiotic fungicides often are produced by bacteria, many of these chemicals likely are produced as one stereoisomer rather than as a mixture. Additionally, at least four of the fungicides are manufactured as single or enriched stereoisomer formulations, which may allow them to be applied at lower rates and/or cost (Williams 1992). They include benalaxyl, diniconazole, furalaxyl, and metalaxyl and are denoted with –M under the "alternate name, isomer" column in Table 2.

Many chiral fungicides are of the ergosterol biosynthesis inhibitor variety and offer both protective and curative properties (Fuchs 1988). Other classes of fungicides were developed closely with the structurally similar herbicides. Interestingly, some of the chiral fungicides also exhibit herbicidal properties, usually with a specific enantiomer displaying either herbicidal or fungicidal action (Burden et al. 1987). Paclobutrazol is one example of a compound that has dual herbicide/fungicide activity. Such compounds are listed by their primary use category as shown in the Pesticide Manual (Mann 2006).

In general, there is a wide assortment of fungicidal compounds, and the enantiomer anti-fungal efficacy of these compounds can vary greatly. One of the more notable compounds is triadimefon, which is converted by fungi into the fungicidally active metabolite triadimenol. In this conversion process, an additional chiral center is formed, and the four resulting enantiomers are produced in different amounts by different species (Deas et al. 1984a, b; Deas et al. 1986).

Fungal species can develop resistance to fungicides, making continual development of new compounds important. This also leads to developing more complex molecules that have a greater chance for chiral centers.

Chirbase, the enantioselective separations database, contains entries for 25 of the 97 fungicides (26%). There are 465 records for these 25 pesticides (431 in LC, 6 in GC, and 28 in CE databases). Diniconazole has the most entries, with 72 total and 69 of those found in the LC database. The number of entries found for each fungicide in each Chirbase database is listed in Table 2. As previously mentioned, Chirbase does not include every published enantioselective separation, but has the most comprehensive information available. The fungicides fenarimol, hexaconazole, imazalil, myclobutanil, nuarimol, penconazole, propiconazole and tebuconazole have no GC entries in Chirbase, but their GC separations are discussed by Bicchi et al. (1999).

4.2 Herbicides

In Table 3, we list 141 chiral herbicides, herbicide safeners, and plant growth regulators and show their structures in Fig. 4 with all possible chiral centers marked. The majority of the compounds have only 1 or 2 chiral features, whereas brassinolide and epocholeone each have 13. Acetochlor, metolachlor, and propisochlor have a bond with restricted rotation leading to atropisomers, which typically are not identified by the MOE software. Amiprofos-methyl, bilanafos, butamifos, DMPA, fosamine and glufosinate have a chiral phosphorous atom, and NC-330 has a chiral sulfur atom. Prototropy (transfer of a proton) between the =O and –OH on the chiral phosphorus atom of glufosinate may be rapidly equilibrated under certain pH conditions, rendering the tautomers difficult, if not impossible, to distinguish by enantioselective techniques. Restrictions in ring configurations may yield smaller numbers of stereoisomers for bicyclic

compounds such as benzobicyclon, brassinolide, cinmethylin, dicyclonon, dikegulac, endothal, epocholeone, gibberellic acid, gibberellins, heptopargil, isonoruron, noruron, profluazol and tetcyclacis. Six herbicides have more than one chiral center, but also a plane of symmetry resulting in a meso-compound, which reduces the number of actual stereoisomers to less than 2^N.

At least 13 of the herbicides are produced as single or enriched stereoisomer formulations. These are noted with S-, -P, or –M in the "Alternate names, isomers" or "Salts, esters" column in Table 3, and include (S)-carvone, dichlorprop-P, diclofop-P-methyl, dimethenamid-P, fenoxaprop-P, flamprop-M, fluazifop-P, glufosinate-P, haloxyfop-P, mecoprop-P, S-metolachlor, quizalofop-P and uniconazole-P. Many of these enriched herbicides belong to the aryloxy- or phenoxypropionic families wherein the R form is the herbicidal enantiomer (Haga et al. 1998). A "chiral switch" occurs when the manufacturer changes from a racemic formulation to an enantioenriched one. The introduction of enantioenriched S-metolachlor to the commercial market was monitored in Swiss lake water samples over a two-year period by enantioselective analysis (Buser et al. 2000).

We have included the herbicide 2,4-D in Table 3 and Fig. 4 as an example of an acid herbicide that can be paired with chiral esters or salts, but the herbicide itself is not chiral. Any achiral acid herbicide that is paired with such chiral moieties will be chiral as long as the bonding is sustained. The pairings, especially the salt forms, may be short-lived following application due to rapid dissociation of the salt moiety or degradation via abiotic and biotic pathways (i.e., ester hydrolysis). For clarity, please see footnotes in the tables for such compounds. The majority of acid herbicides and other acid functional pesticides covered in this review contain a parent group moiety that is chiral (e.g., 3,4-DP), but these pesticides may contain additional chiral centers (and thus stereoisomers) that depend on the formulation. We

have noted some of the more common ester and salt forms in the tables, but these listings are not comprehensive.

The mode of action of many herbicides is to interfere with chiral plant hormones controlling growth, so it is not surprising that the absolute configuration of the pesticides plays a role in efficacy (Naber and van Rensen 1988). The degradation of dichlorprop and mecoprop by soil microbes is enantioselective, because two different enzymes each metabolize one enantiomer (Zipper et al. 1996; Nickel et al. 1997; Kohler et al. 1998; Zipper et al. 1998; Müller and Babel 1999). These two examples demonstrate how the degradation is different between stereoisomers, and this, when combined with stereospecific toxicity, can affect not only efficacy, but also exposure and risk to humans and the environment.

Chirbase contains entries for 44 of the 141 herbicides (31%). There are 972 records for these 44 pesticides (766 in LC, 120 in GC, and 86 in CE databases). Carvone has the most entries, with a total of 91, of which 76 are found in the GC database. The remaining compounds found in Chirbase are shown in Table 3. The four stereoisomers of the paclobutrazol were separated by GC (Clark and Deas 1985), and the enantiomers of cloprop were separated by CE (Tang et al. 2005). Neither of these example herbicides is found as entries in Chirbase.

4.3 Insecticides

In Table 4, we list 149 chiral insecticides, and show their structures in Fig. 5. Thirty-three insect attractants, pheromones, repellents, and insecticide synergists were included in the miscellaneous category and will be discussed in the next section. The majority of the insecticides have one to four chiral features, but several biologically-derived insecticides (e.g., abamectin, allosamidin, azadirachtin, emmamectin, sabadilla, spinetoram and spinosad) have more than a

dozen chiral features. Twenty-seven insecticides are chiral at a phosphorus atom (see Figs. 2 and 5), which is not surprising considering that the organophosphorus (OP) pesticides are included in this group. The following compounds all have a chiral sulfur atom in their structure: 2,2-dichlorovinyl 2-ethylsulfinylethyl methyl phosphate, ethiprole, fipronil, IPSP, mesulfenfos, oxydemeton-methyl, oxydeprofos, oxydisulfoton, and sulfoxaflor. α-Hexachlorocyclohexane (HCH) is an example of a molecule that does not contain a point or plane of symmetry, thus it is chiral and has two enantiomers (see Fig. 2D). The other six isomers of HCH, including the active insecticidal form, γ-HCH or lindane, are achiral (Willett et al. 1998).

There are many chiral insecticides that have ring-constrained chiral features, which limits the actual number of possible stereoisomers. For example, the organochlorine (OC) insecticide chlordane has six chiral carbon atoms, but only two of them are unconstrained (see Fig. 2F), which leads to four possible stereoisomers, a pair of enantiomers for *cis*-chlordane and a pair for *trans*-chlordane. Constrained and meso-compounds are noted in Table 4.

At least 17 of the chiral insecticides are produced as single or enriched stereoisomer formulations, including allethrin, cyfluthrin, cyhalothrin, cypermethrin, cyphenothrin, deltamethrin, d-limonene, endosulfan, fenvalerate, fluvalinate, hydroprene, kinoprene, methoprene, permethrin, phenothrin, resmethrin and tetramethrin. For some of the pyrethroid insecticides, multiple commercial formulations have been progressed from a racemic mixture to increased enrichment of the active stereoisomer(s) (Williams 1992). Indeed, deltamethrin was specifically developed as a single stereoisomer formulation (Carle et al. 1982).

Organochlorine pesticides are among the most widely studied classes of chiral environmental contaminants to date (Bethan et al. 1997; Ridal et al. 1997; Ulrich and Hites 1998; Vetter et al. 1999; Garrison et al. 2000). Although most of these compounds were banned in the

1980s if not before, their persistence in the environment makes them interesting to study even today (Kurt-Karakus et al. 2007). Enantiomer analysis of these chemicals is often difficult due to the complex mixtures of the technical products. Many of the 32,768 theoretically possible configurations of toxaphene are chiral; chromatographic separation of single compounds in the mixture is very challenging, and avoiding coelutions for stereoisomer separations is also difficult (Vetter 1993). Despite this hurdle, chiral gas chromatographic separation has been accomplished for a few compounds in this complex pesticide mixture (Vetter et al. 1997; Kallenborn and Hühnerfuss 2001).

The organophosphorus pesticides were developed in the 1950s and have been used against plant diseases, insects, and weeds (Sasaki 1998). Their mode of action typically is through acetylcholine esterase inhibition (Kurihara et al. 1997). This group of pesticides is particularly interesting from a stereochemical standpoint, because a chiral center may be present at a phosphorus atom, carbon atom, or even at a sulfur atom. Some OP compounds are converted into oxon degradation products by replacing the phosphorus bonded sulfur atom with oxygen (Lee et al. 1978; Nomeir and Dauterman 1979; Hirashima et al. 1989; Berkman et al. 1993). These oxon degradates are often the more toxic and insecticidally active form, and some are chiral (fonofos oxon, EPN oxon, malaoxon, salioxon, etc.). The efficacy of the stereoisomers depends on their structure, with phosphorus chirality making a greater impact on the variation in activity than does carbon chirality (Williams 1992; Buser and Francotte 1997). The difference between stereoisomer activities ranges from a factor of 1.5 to 20 or more (Sasaki 1998).

The pyrethroid insecticides are synthetic variants of the natural products found in chrysanthemum flowers. These compounds are neurotoxic, causing knockdown and mortality effects (Vijverberg and Oortgiesen 1988). Since allethrin, the first pyrethroid, was developed in

1949, advances have been made to make these compounds more photostable, less toxic to mammals, and good alternatives to more toxic legacy pesticides (Williams 1992). Pyrethroids usually have several chiral centers, often at the cyclopropane ring, creating multiple stereoisomers that have varying degrees of toxicity (Chamberlain et al. 1998). The nomenclature for this class lacks uniformity and is sometimes confusing, because single or enriched stereoisomer formulations often have names similar to those of compounds having unspecified stereochemistry. For example, fenvalerate is a racemic mix of four stereoisomers, whereas esfenvalerate is ≥ 75% resolved (S,S)- isomers; resmethrin is 20–30% (1RS)-*cis*- and 80–70% (1RS)-*trans*- isomers, whereas bioresmethrin is ≥ 90% (1R)-*trans*- isomer and ≤ 3% *cis*-isomers; a similar formulation pattern exists for cypermethrin and α-, β-, θ-, or ζ-cypermethrin. Additionally, the cyano group of the type II pyrethroids is not stereochemically stable, and can invert/isomerize under high temperature or in polar protic solvents with light (Ruzo et al. 1977; Liu et al. 2005; Qin and Gan 2007). This inversion can be problematic for chiral analyses, because liquid or supercritical fluid chromatography often utilize protic solvents, like alcohols, for the mobile phase.

Chirbase contains entries for 50 of the 149 insecticides (34%, see Table 4). There are 1066 records for these 50 pesticides (706 in LC, 344 in GC, and 16 in CE databases). d-Limonene has the most entries, with a total of 175 of which all but 7 are found in the GC database. Several OC, OP, and pyrethroid insecticides (such as chlordane, phenthoate, and allethrin) are among those in Chirbase. These insecticides have been used extensively, are well studied by achiral techniques, and have successful enantioselective separation techniques developed and ready to use. However, Chirbase does not have any GC entries for fipronil, although it has been separated using enantioselective chromatography (Konwick et al. 2005).

4.4 Miscellaneous other Pesticides

In Table 5, we list 95 other miscellaneous pesticides, note the primary pesticidal uses, and show their structures in Fig. 6. This grouping includes acaricides, bactericides, bioirritants, chemosterilants, insect attractants, insect pheromones, insect repellents, insecticide synergists, mammal repellents, nematicides, other, rodenticides and virucides. The majority of these compounds have one to six chiral features, but there are several avermectin pesticides that have up to 20 chiral features. The following compounds all have a chiral phosphorus atom in their structure: amidothioate, fenamiphos, fosthiazate, imicyafos, isamidofos, phosphocarb, and trifenofos. The following compounds all have a chiral sulfur atom in their structure: acetoprole, aramite, fensulfothion, propargite, and sulfoxide.

In Fig. 6, all possible chiral centers have been marked, but for compounds with fused rings, there will be fewer possible stereoisomers. Compounds with such constraints or meso forms are noted in Table 5. Because some of the large molecules are produced biologically, these chemicals probably are produced as single stereoisomers rather than as mixtures. No additional single or enriched formulations are noted in Table 5.

Although the insect attractants, pheromones, and repellents are fairly simple molecules, stereochemistry plays a particularly important role, because these compounds commonly interact with specific biological molecules (Borden et al. 1976; Vité et al. 1976; Payne et al. 1982; Mori 1997). For example, *Dendroctonus brevicomis* (western pine beetle) was more attracted to the (+) enantiomer of exo-brevicomin and the (–) enantiomer of frontalin than to their antipodes. There were also sex differences, with females exhibiting greater attraction to all exo-brevicomin treatments, especially the (–) enantiomer [the male/female ratio attracted was 0.92 for the

racemic mixture, 0.85 for the (+) enantiomer, and 0.58 for the (–)] (Wood et al. 1976). Population and species differences also have been noted; *Ips pini* East (pine engraver) were attracted more to a mixture of ipsdienol enantiomers, whereas *Ips pini* West were attracted more to (–)-ipsdienol. *Ips paraconfusus* (California fivespined) was attracted more to (+)-ipsdienol, when in combination with other pheromone components (Mustaparta et al. 1980).

Chirbase contains entries for 27 of the 95 miscellaneous pesticides (28%, see Table 5). There are 1,029 records for these 27 pesticides (774 in LC, 182 in GC, and 73 in CE databases). Warfarin has the most entries, with a total of 624 most of these are in the LC database. Warfarin, an anticoagulant rodenticide, is used pharmaceutically as the blood thinner coumadin. Because warfarin has medicinal uses, much is known about the efficacy (Eble et al. 1966), separation (De Vries and Völker 1989), and metabolism (Park 1988) of its enantiomers. Again, Chirbase does not contain all published stereoisomer separations, so readers are encouraged to perform a thorough literature search for chromatographic methods prior to undertaking research on any specific chiral pesticide.

5 Summary

Of the 1,693 pesticides considered in this review, 1,594 are organic chemicals, 47 are inorganic chemicals, 53 are of biological origin (largely non-chemical; insect, fungus, bacteria, virus, etc.), and 2 have an undetermined structure. Considering that the EPA's Office of Pesticide Programs found 1252 active pesticide ingredients (personal communication), we consider this dataset to be comprehensive; however no direct comparison of the compound lists was undertaken. Of all pesticides reviewed, 482 (28%) are chiral; 30% are chiral when considering only the organic chemical pesticides. A graph of this distribution is shown in Fig. 7A. Each pesticide is classified with up to three pesticidal utilities (e.g., fungicide, plant growth regulator,

rodenticide, etc.), taken first from the Pesticide Manual as a primary source, and the Compendium of Common Pesticide Names website as a secondary source. Of the chiral pesticides, 195 (34%) are insecticides (including attractants, pheromones, and repellents), 150 (27%) are herbicides (including plant growth regulators and herbicide safeners), 104 (18%) are fungicides, and 55 (10%) are acaricides. The distribution of chiral pesticides by utility is shown in Fig. 7B, including categories of pesticides that make up 3% or less of the usage categories. Fig. 7C shows a similar distribution of non-chiral pesticide usage categories. Of the chiral pesticides, 270 (56%) have one chiral feature, 105 (22%) have two chiral features, 30 (6.2%) have three chiral features, and 29 (6.0%) have 10 or more chiral features. ChirBase contains more than 3,500 records for 146 of the 482 chiral pesticides (30%). The majority of the records are found in the liquid chromatography database (2,677 or 76%), followed by the gas chromatography database (652 or 18%), and the capillary electrophoresis database (203 or 6%).

Chiral chemicals pose many difficulties in stereospecific synthesis, characterization and analysis. When these compounds are purposely put into the environment, even more interesting complications arise in tracking, monitoring, and predicting their fate and risks. More than 475 pesticides are chiral, as are other chiral contaminants such as pharmaceuticals, PCBs, brominated flame retardants, synthetic musks, and their degradates (Kallenborn and Hühnerfuss 2001; Heeb et al. 2007; Hühnerfuss and Shah 2009). The stereoisomers of pesticides can have widely different efficacy, toxicity to non-target organisms, and metabolic rates in biota. For these reasons, it is important to first be aware of these fate and effect differences, to incorporate molecular asymmetry insights into research projects, and to study the individual stereoisomers of the applied pesticide material.

With the advent of enantioselective chromatography techniques, the chirality of pesticides have been studied increasingly. However, only 30% of the chiral pesticides covered in this review have entries in ChirBase (Advanced Chemistry Development 1997–2010), highlighting the need for expanded efforts to develop additional enantioselective chromatographic methods. Other techniques (e.g., nuclear magnetic resonance, spectroscopy) are available for investigation of chiral compounds, but often are not utilized because of cost, complexity, or simply not recognizing that a pesticide is chiral. In this review, we have listed and briefly described the general nature of chiral fungicides, herbicides, insecticides and miscellaneous other classes. A dataset generated for this review contains 1,693 pesticides, the number of enantioselective separation records in ChirBase, pesticide usage class, SMILES structure string and counts of stereogenic centers. This dataset is publically available for download at the following website: http://www.epa.gov/heasd/products/products.html. With the information herein coupled to the publically accessible dataset we can begin to develop the tools to handle molecular asymmetry as it applies to agrochemicals. Additional structure-based resources may be needed to allow further analysis of key parameters (e.g., exposure, toxicity, environmental fate, degradation and risks) for individual stereoisomers of chiral compounds.

Comment [EMU1]: Please contact the corresponding author before publishing to ensure this URL is correct.

Acknowledgments and Disclaimer

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to review and approved for publication by the U.S. EPA and USGS. Any use of trade, product, or firm names in this publication is for descriptive purposes only and does not imply endorsement by the U.S. Government.

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Fig. captions

Fig. 1 Dataset curation, sources of information and compilation procedure

A. Dataset construction and chemical structure assessment

B. Chiral pesticide processes

Fig. 2 Examples of the types of chirality (A–D) and special cases (E–F) encountered in pesticides

A Chiral center at carbon noted by an asterisk (*) in chiral structures

B Chiral sulfur atom noted by an asterisk (*) in chiral structures. Example: Fipronil

C Atropisomers caused by hindered rotation about a bond. Atropisomers will be noted by a curved arrow in chiral structures. Example: Acetochlor

D No plane or point of symmetry noted by a dagger (†) in chiral structures. Example: Hexachlorocyclohexane, a= axial, e= equatorial. The boat configuration and asymmetric chlorine placement cause chirality in this molecule.

E Meso compounds are noted in the tables. Example: 3,4-dichlorotetrahydrothiophene 1,1 dioxide has R,R and S,S enantiomers; but R,S and S,R are identical (superimposable) structures and constitute the meso-compound.

F Constrained fused rings are noted in the tables. Example: Chlordane has two unconstrained (*) and four constrained (≠) chiral centers, thus four possible stereoisomers, i.e., two *cis*- and two *trans*-enantiomers.

Fig. 3 Chiral fungicide structures. See Fig. 2 for symbol description

Fig. 4 Chiral herbicide, herbicide safener, and plant growth regulator structures. See Fig. 2 for symbol description

Fig. 5 Chiral insecticide structures. See Fig. 2 for symbol description

Fig. 6 Miscellaneous chiral pesticide structures. See Fig. 2 for symbol description

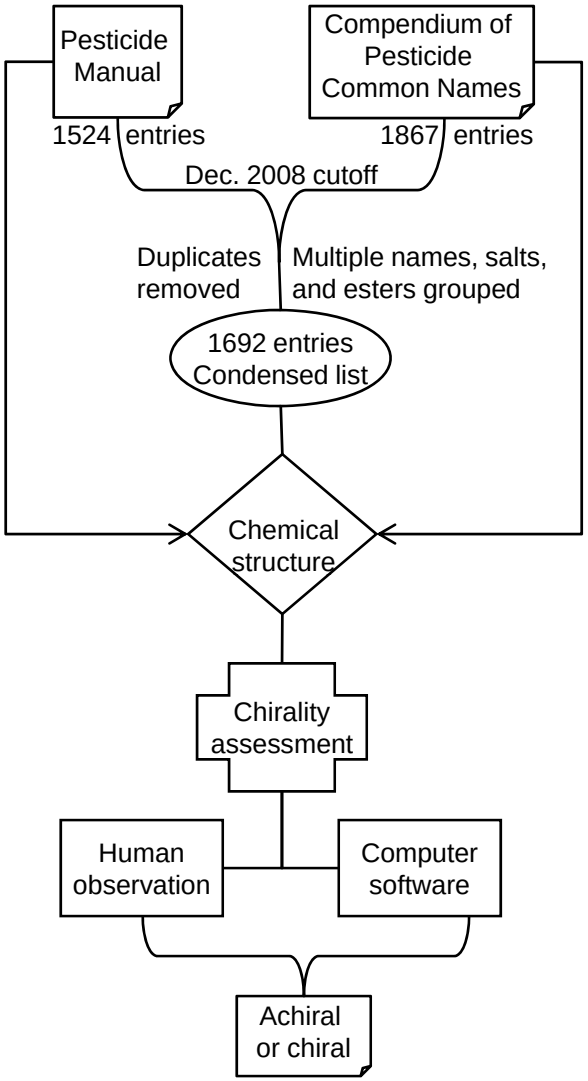
Fig. 7 Pesticide type (chiral and achiral organic, inorganic, biological) and utility statistics

A General pesticide type for 1,693 dataset entries

B 482 chiral pesticides by specific utility

C 1,211 achiral pesticides by specific utility

A.


Pesticide Manual
Compendium of Pesticide Common Names
1524 entries
1867 entries
Dec. 2008 cutoff
Duplicates removed
Multiple names, salts, and esters grouped
1692 entries Condensed list
Chemical structure
Chirality assessment
Human observation
Computer software
Achiral or chiral

B.

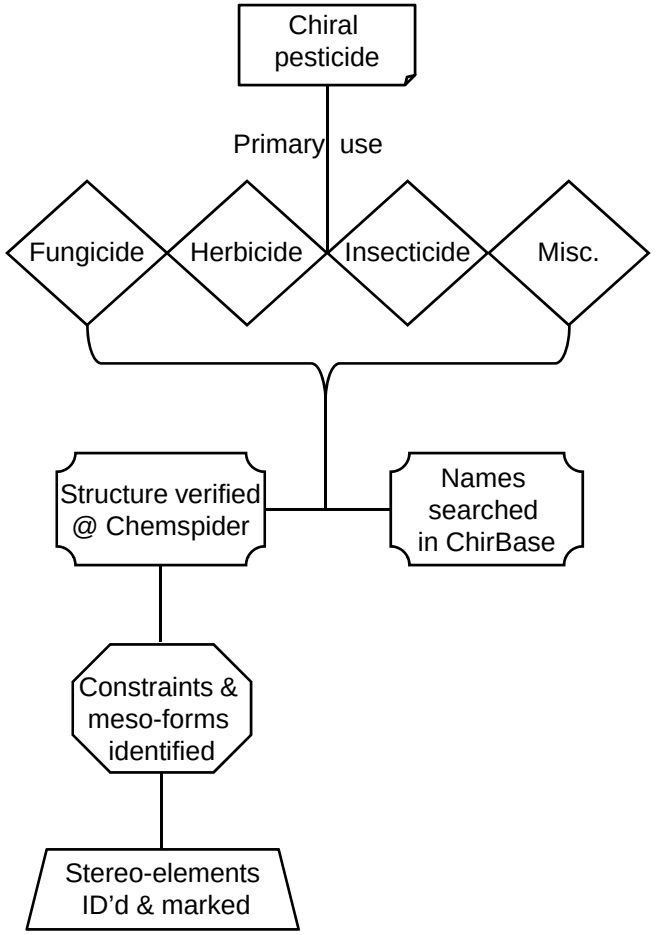
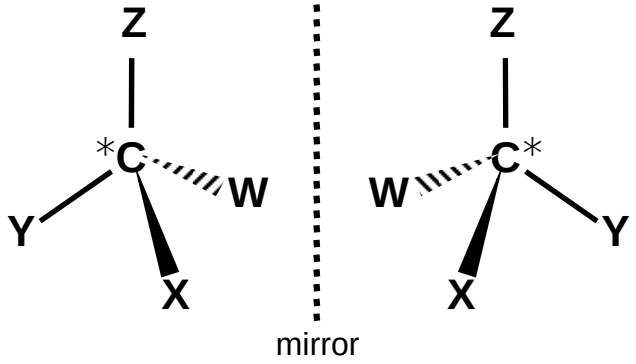

Chiral pesticide
Primary use
Fungicide
Herbicide
Insecticide
Misc.
Structure verified @ Chemspider
Names searched in ChirBase
Constraints & meso-forms identified
Stereo-elements ID'd & marked

Fig. 1

A.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C
W
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mirror
Z
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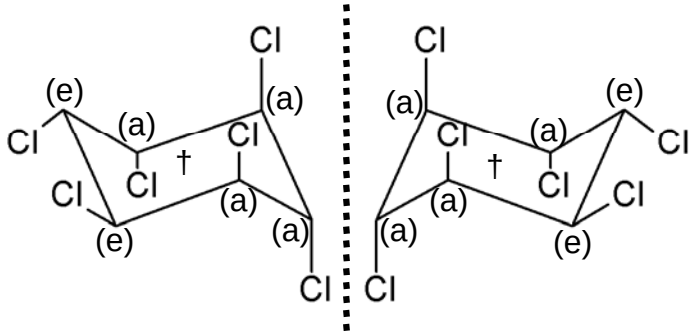
W
Y
X

D.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(a)
Cl
(a)
Cl
†
Cl
Cl
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(a)
Cl
Cl
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Cl
†
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Cl
(e)
(a)
Cl
Cl
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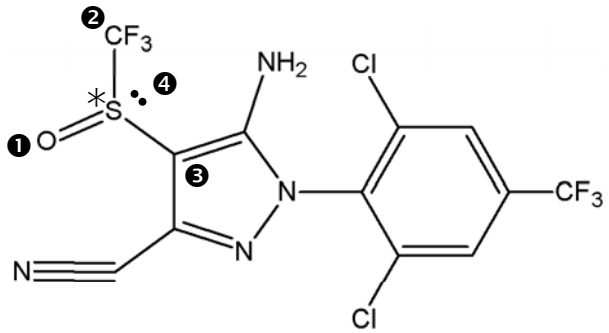
B.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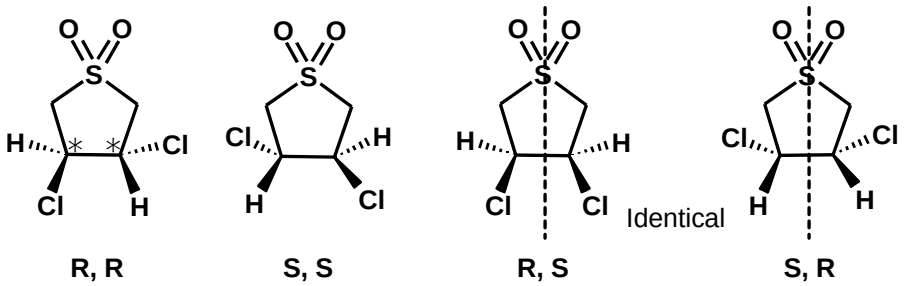
CF3
NH2
Cl
❹
S
❶
O
❸
N
CF3
N
N
Cl

E.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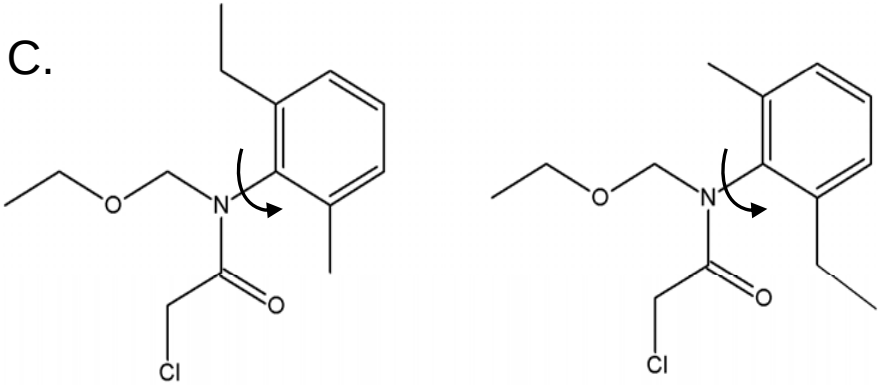
O
S
H
Cl
Cl
H
R, R
S, S
R, S
Identical
S, R

C.


O
N
O
Cl
O
N
O
Cl

F.

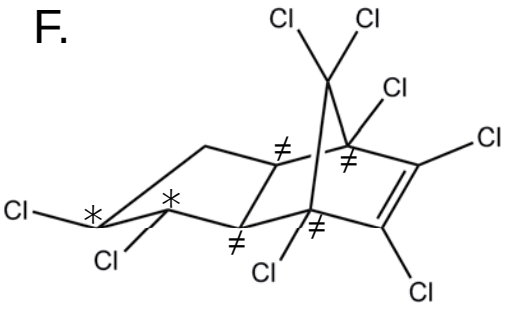

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Fig. 2

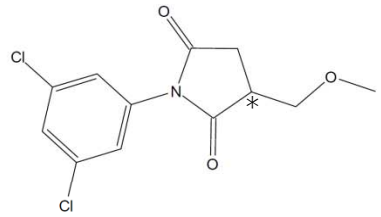
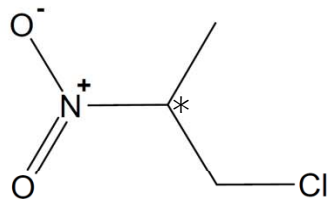
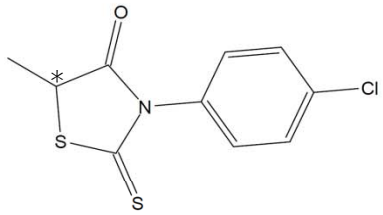
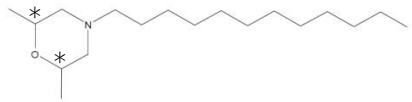
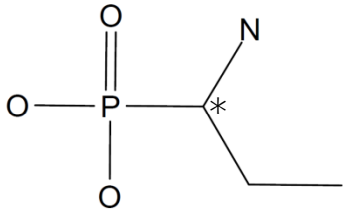
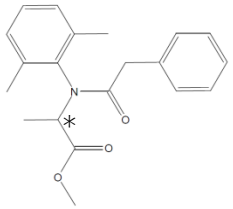
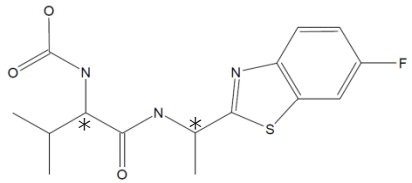
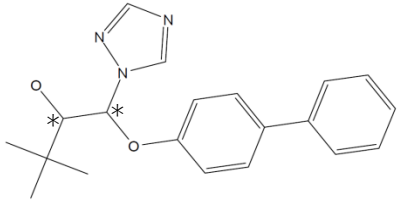
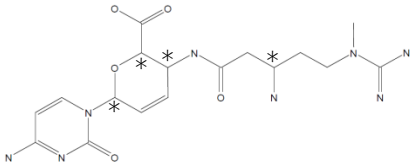
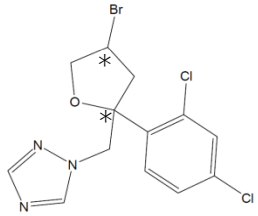
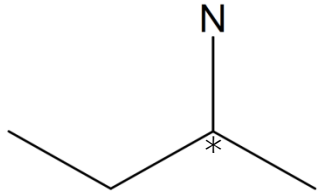
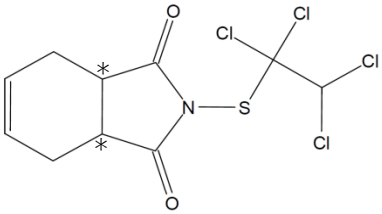
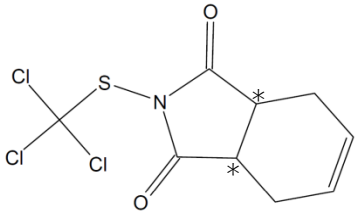
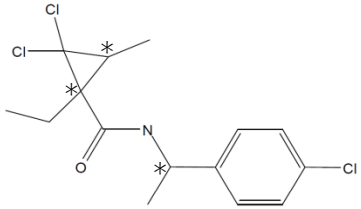
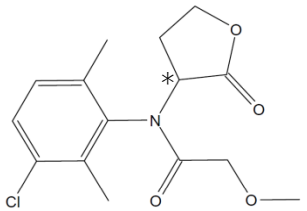
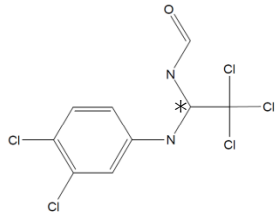
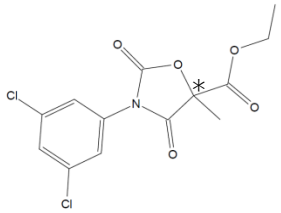
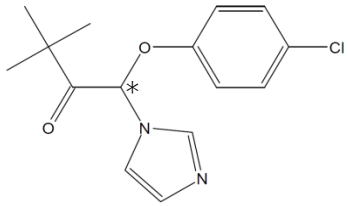
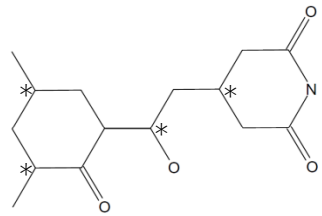
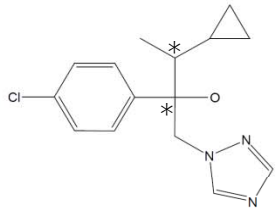
 (RS)-N-(3,5-dichlorophenyl)-2-(methoxymeth..	 1-chloro-2-nitropropane	 3-(4-chlorophenyl)-5-methylrhodanine	 aldimorph
 ampropylfos	aureofungin A $C_{59}H_{86}O_{19}$ aureofungin B $C_{57}H_{85}O_{19}$ aureofungin	 benalaxyl	 benthiavalicarb
 bitertanol	 blasticidin-S	 bromuconazole	 butylamine
 captafol	 captan	 carpropamid	 CGA 80000
 chloraniformethan	 chlozolinate	 climbazole	 cycloheximide

Fig. 3, page 1



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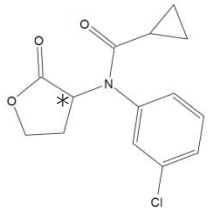

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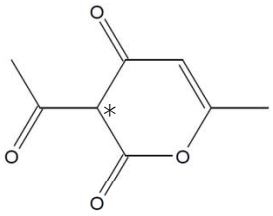

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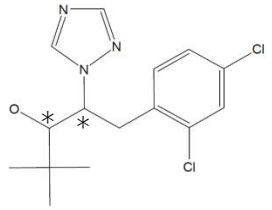

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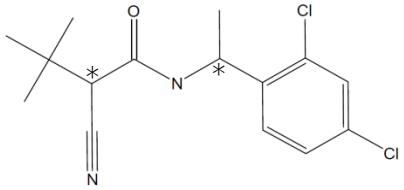

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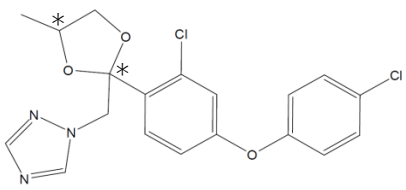

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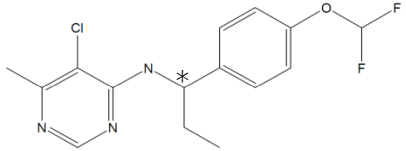

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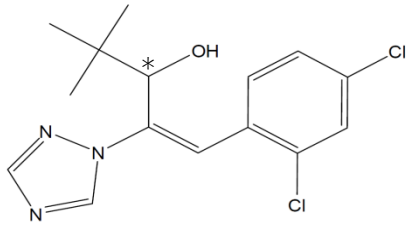

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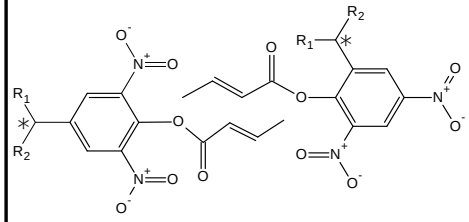
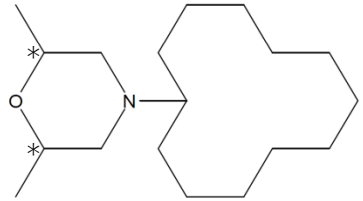


dinocap

R^1= methyl, ethyl, propyl R^2= hexyl, pentyl, butyl



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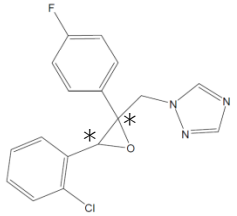

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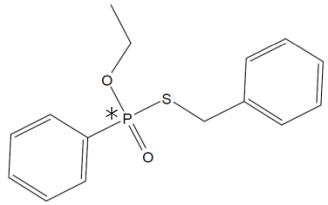

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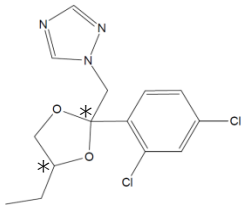

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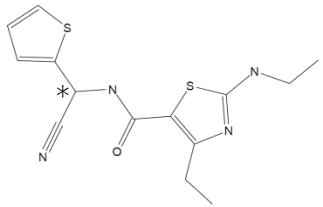

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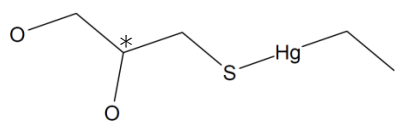

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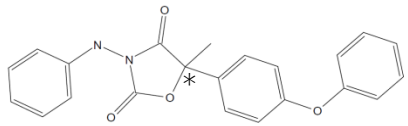

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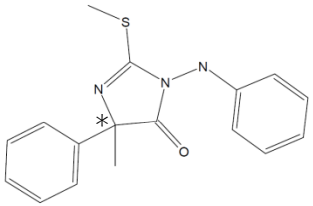

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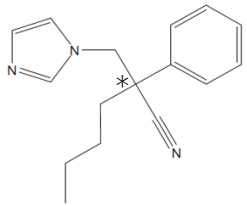

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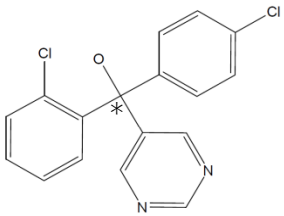

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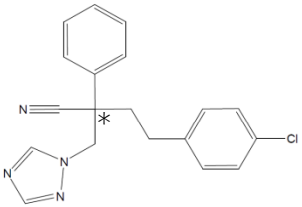
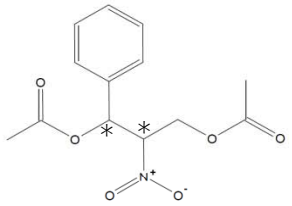


fenbuconazole

Fig. 3, page 2



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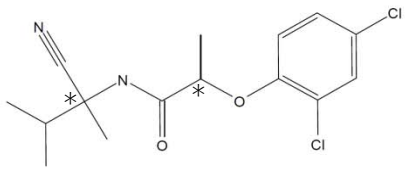

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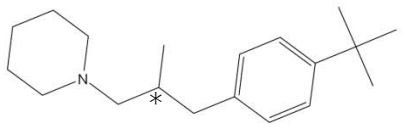

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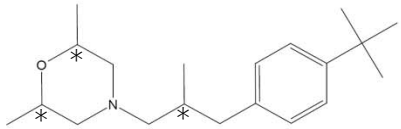

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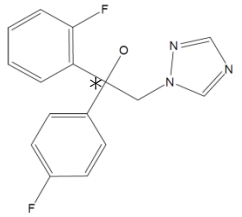

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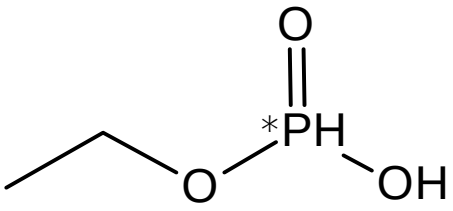

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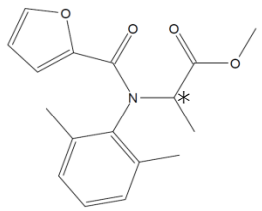

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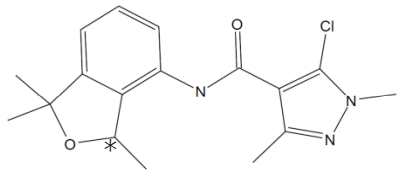

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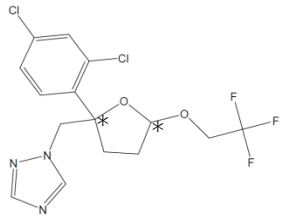

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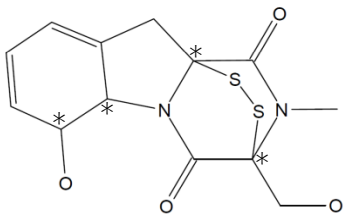

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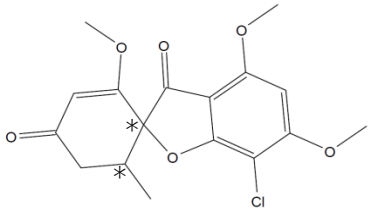

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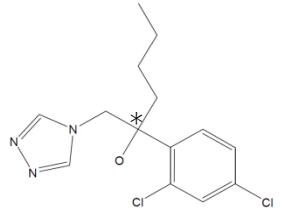

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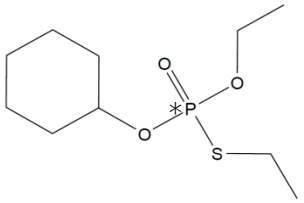

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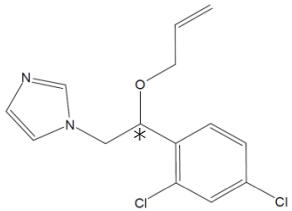

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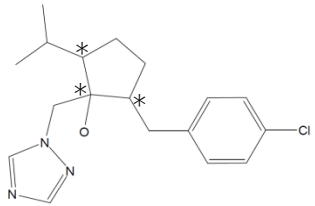

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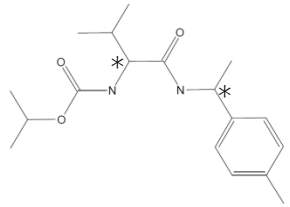

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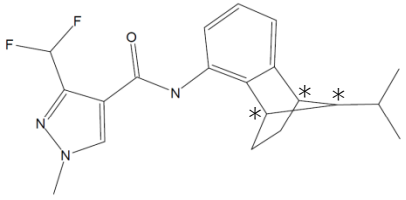

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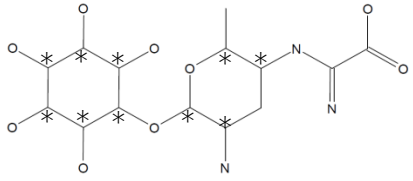

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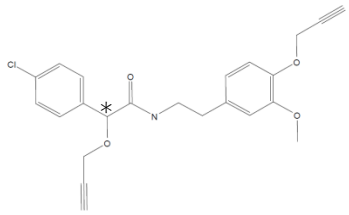

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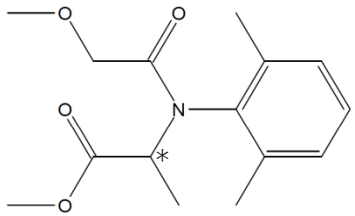
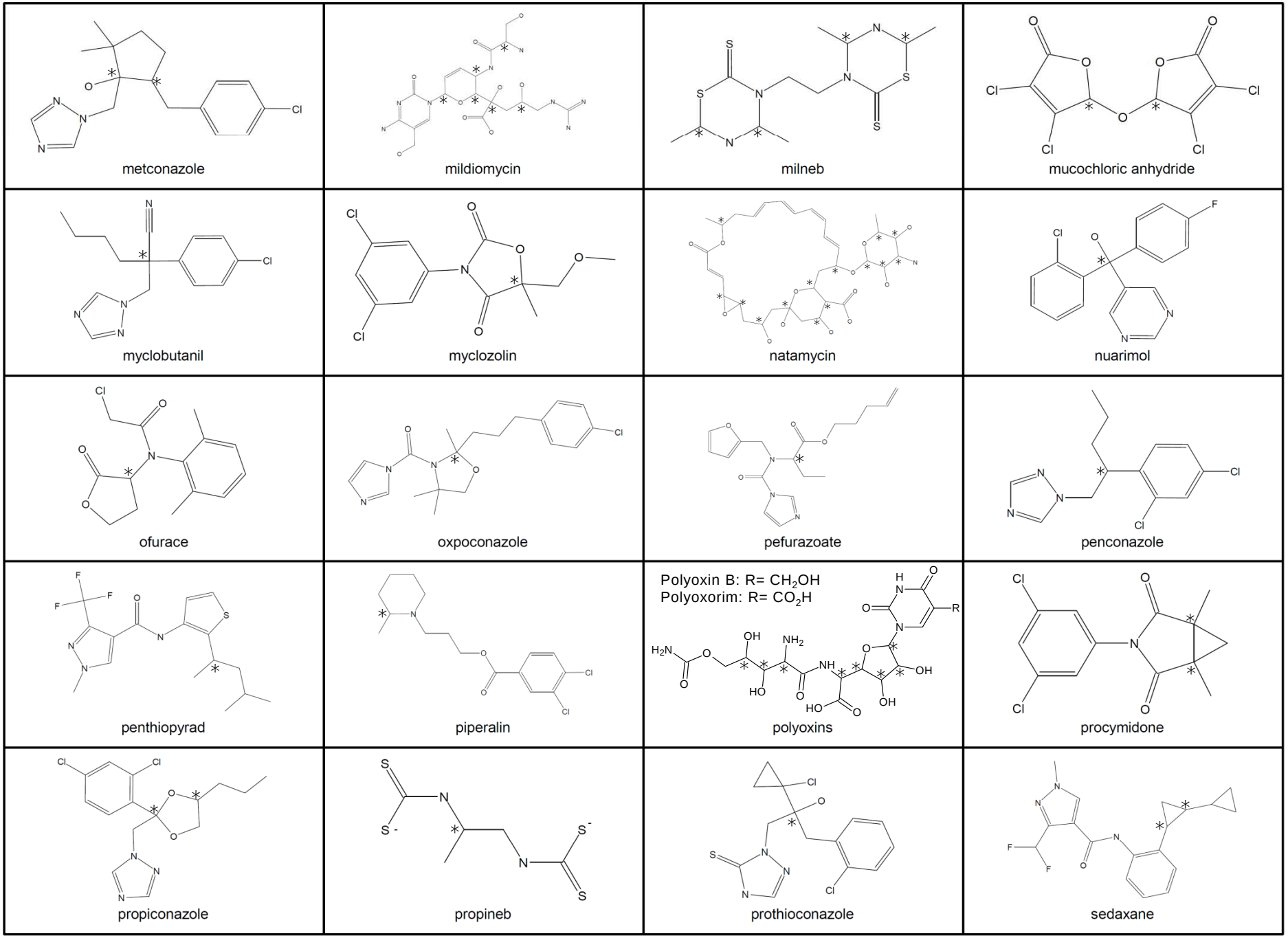


metalaxyl

Fig. 3, page 3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milneb
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myclobutanil
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penconazole
penthiopyrad
piperalin
Polyoxin B: R= CH2OH
Polyoxorim: R= CO2H
polyoxins
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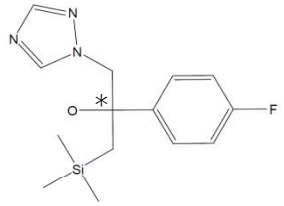
propiconazole
propineb
prothioconazole
sedaxane

Fig. 3, page 4



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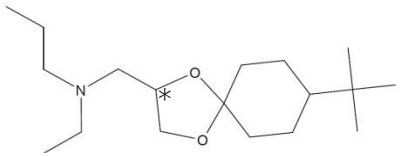

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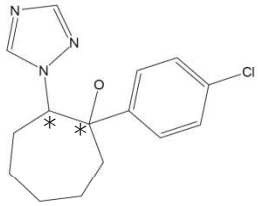
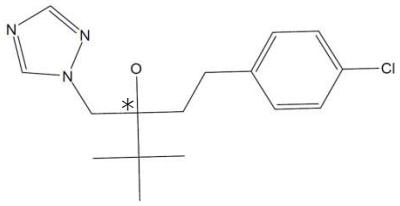


SSF-109



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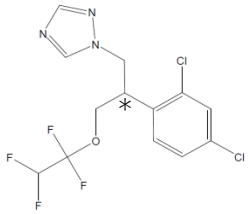

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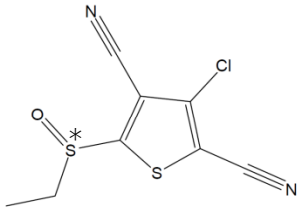

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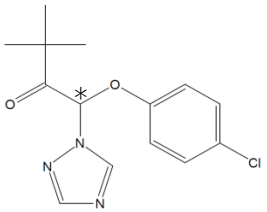

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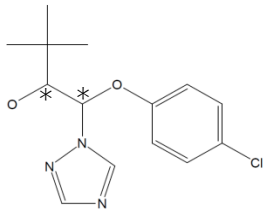

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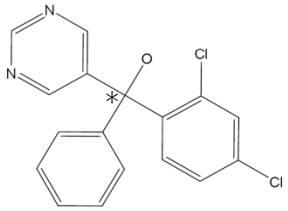

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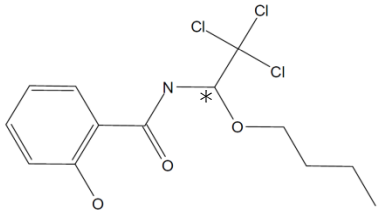

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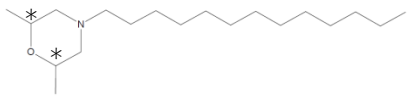

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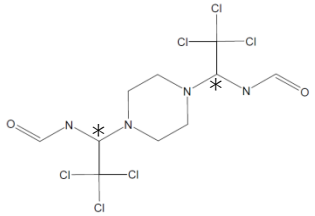

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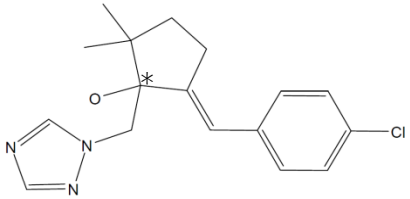

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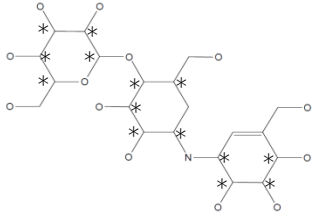

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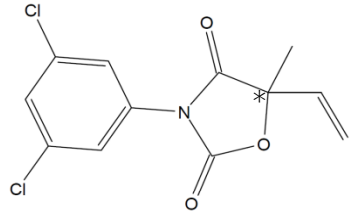

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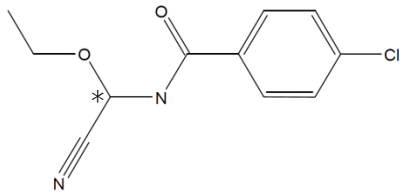

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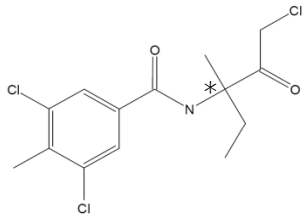

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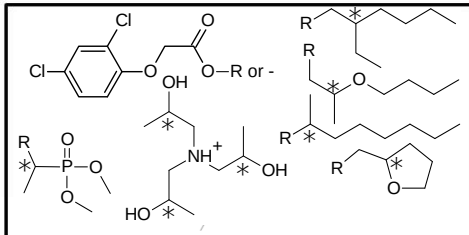
Fig. 3, page 5



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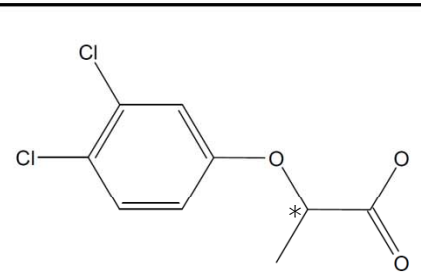

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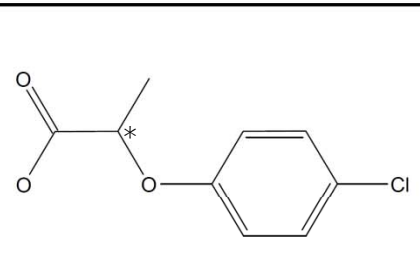

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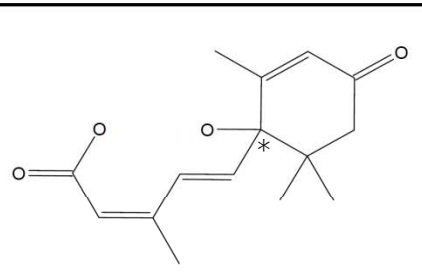

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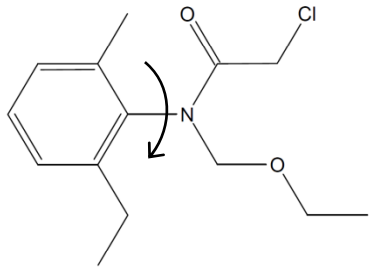

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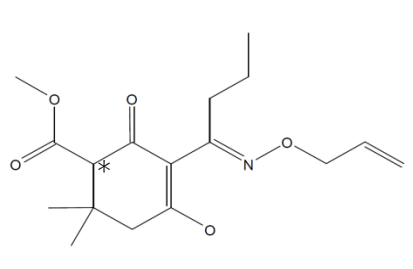

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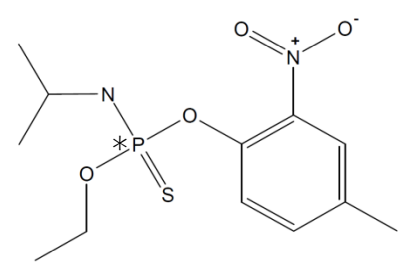

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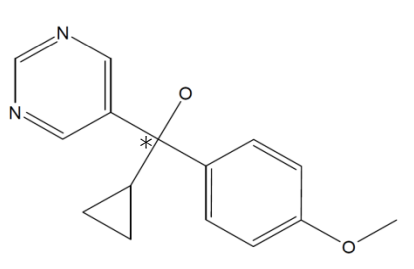

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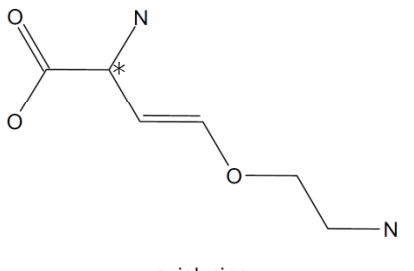

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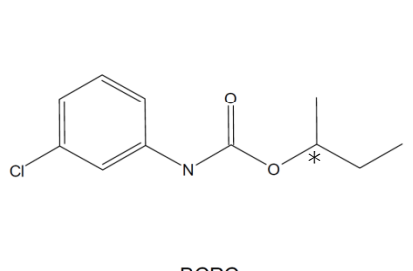

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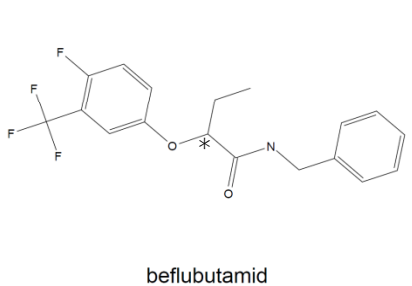

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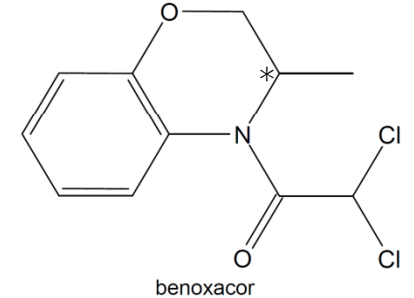

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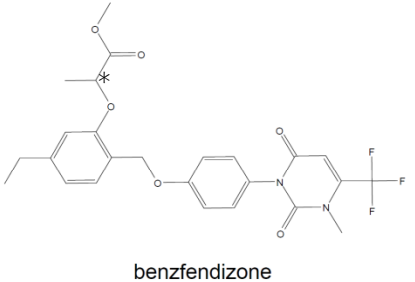

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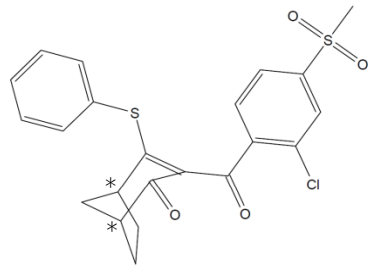

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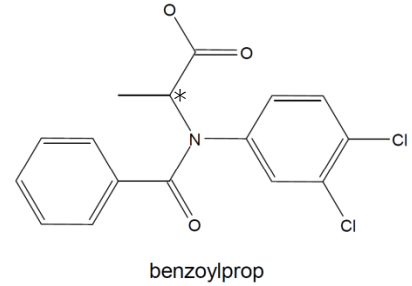

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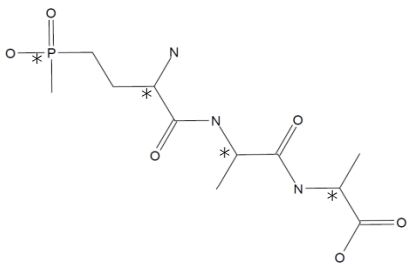

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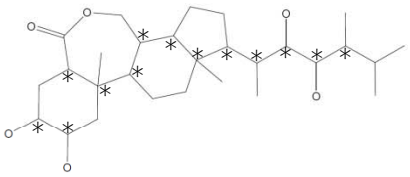
Fig. 4, page 1



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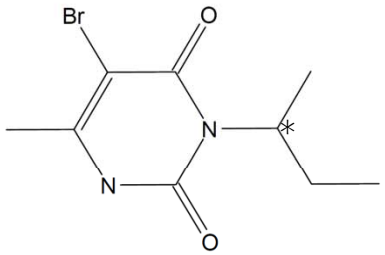

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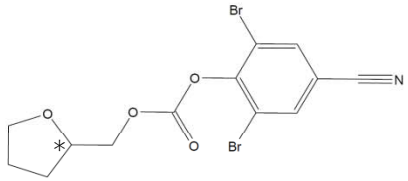

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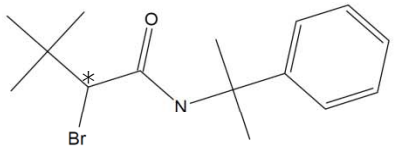

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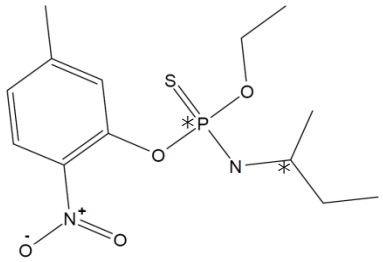

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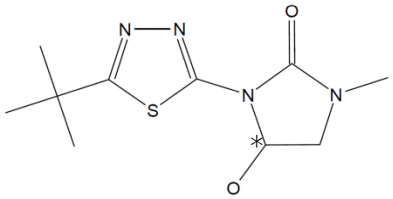

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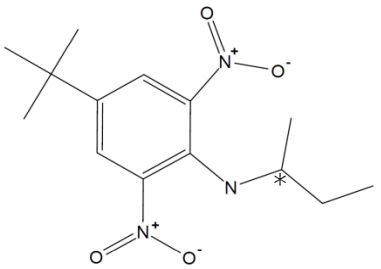

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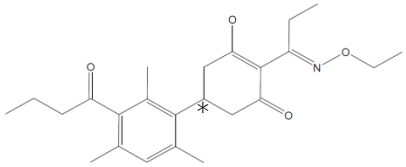

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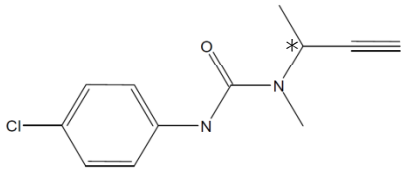

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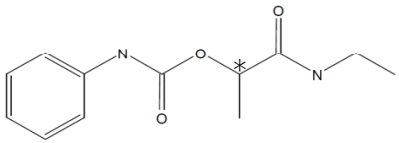

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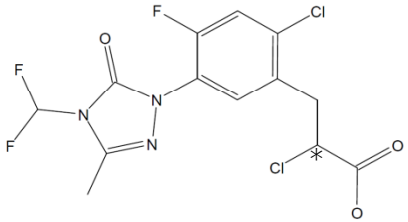

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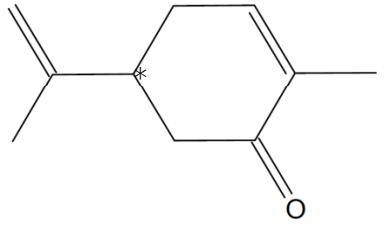

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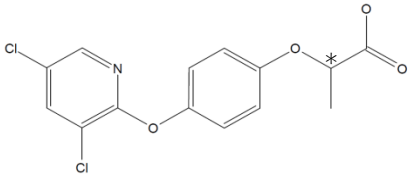

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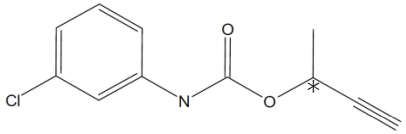

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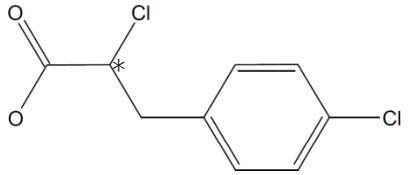

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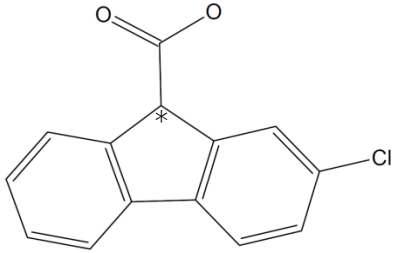
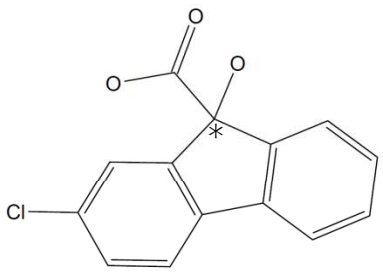


chlorfluren

Fig. 4, page 2



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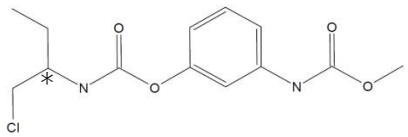

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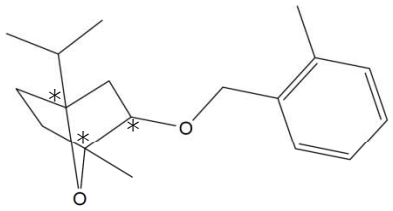

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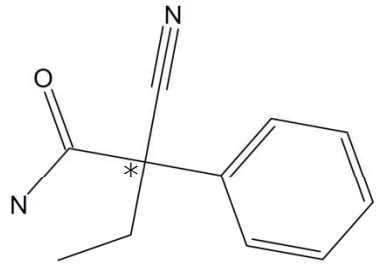

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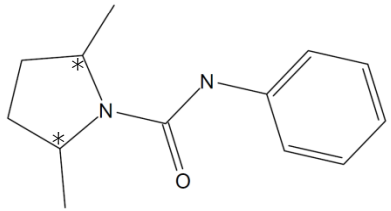

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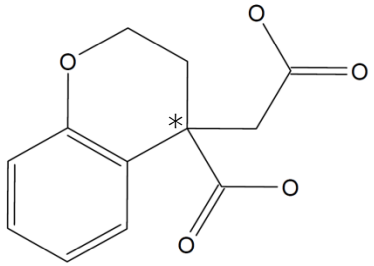

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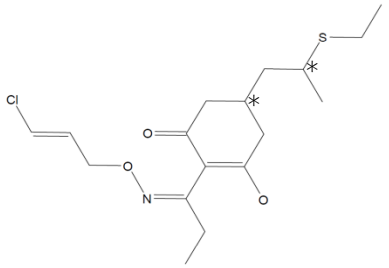

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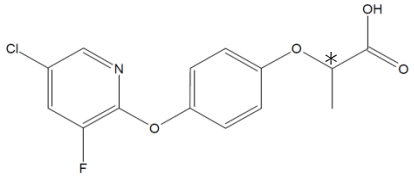

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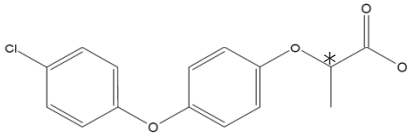

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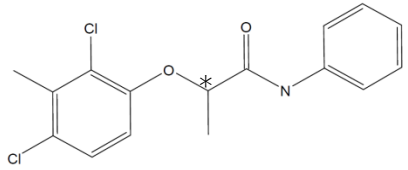

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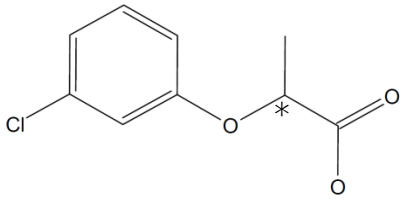

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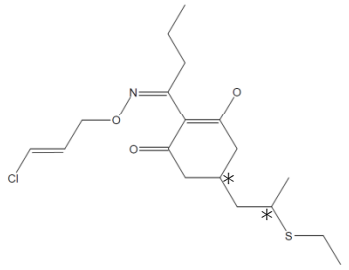
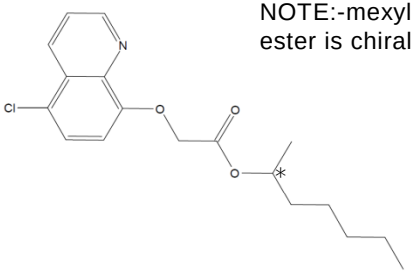


cloproxydim

NOTE:-mexyl ester is chiral



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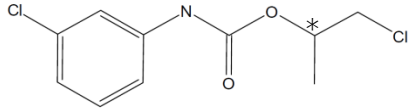

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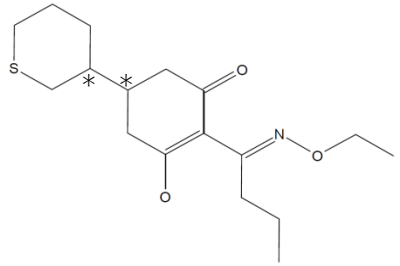

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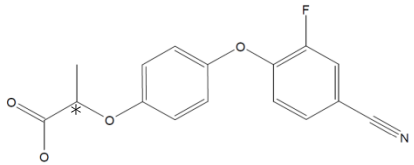

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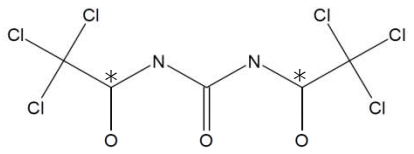
Fig. 4, page 3



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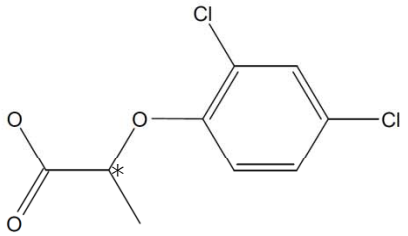

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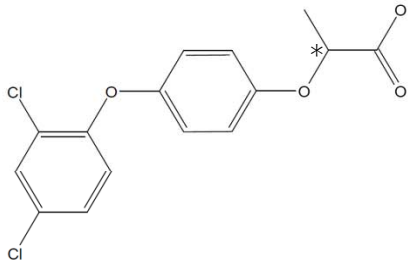

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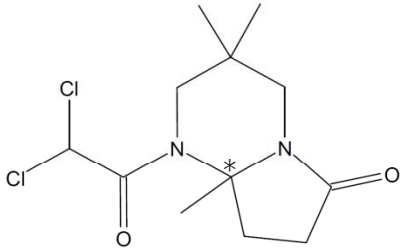

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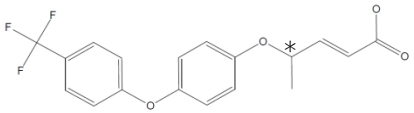

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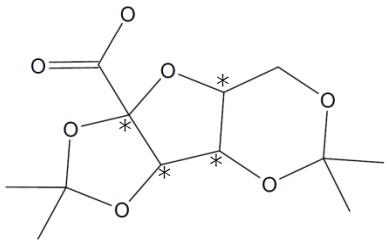

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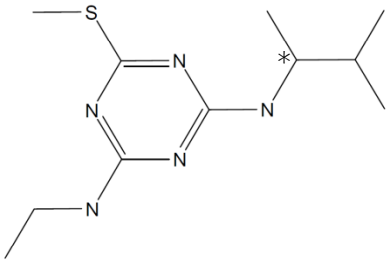

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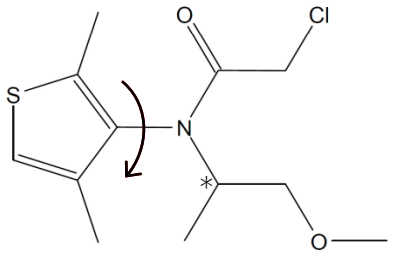

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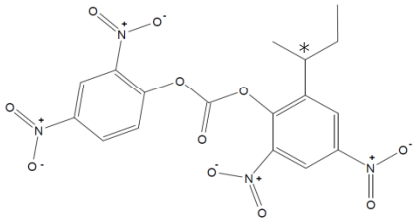

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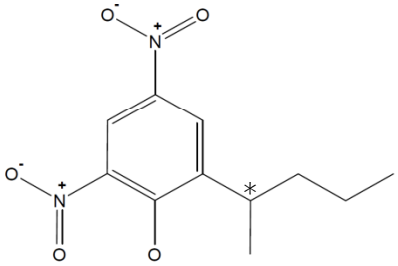

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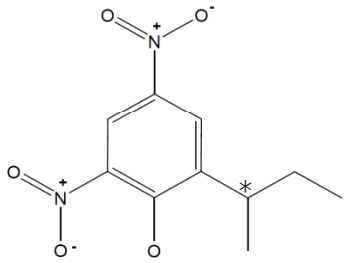

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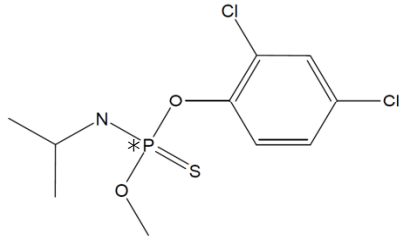

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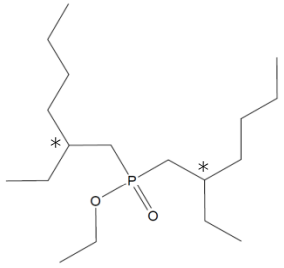

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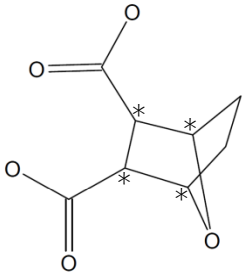

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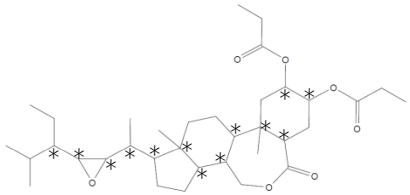

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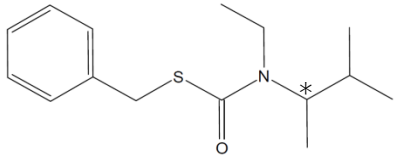

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Fig. 4, page 4

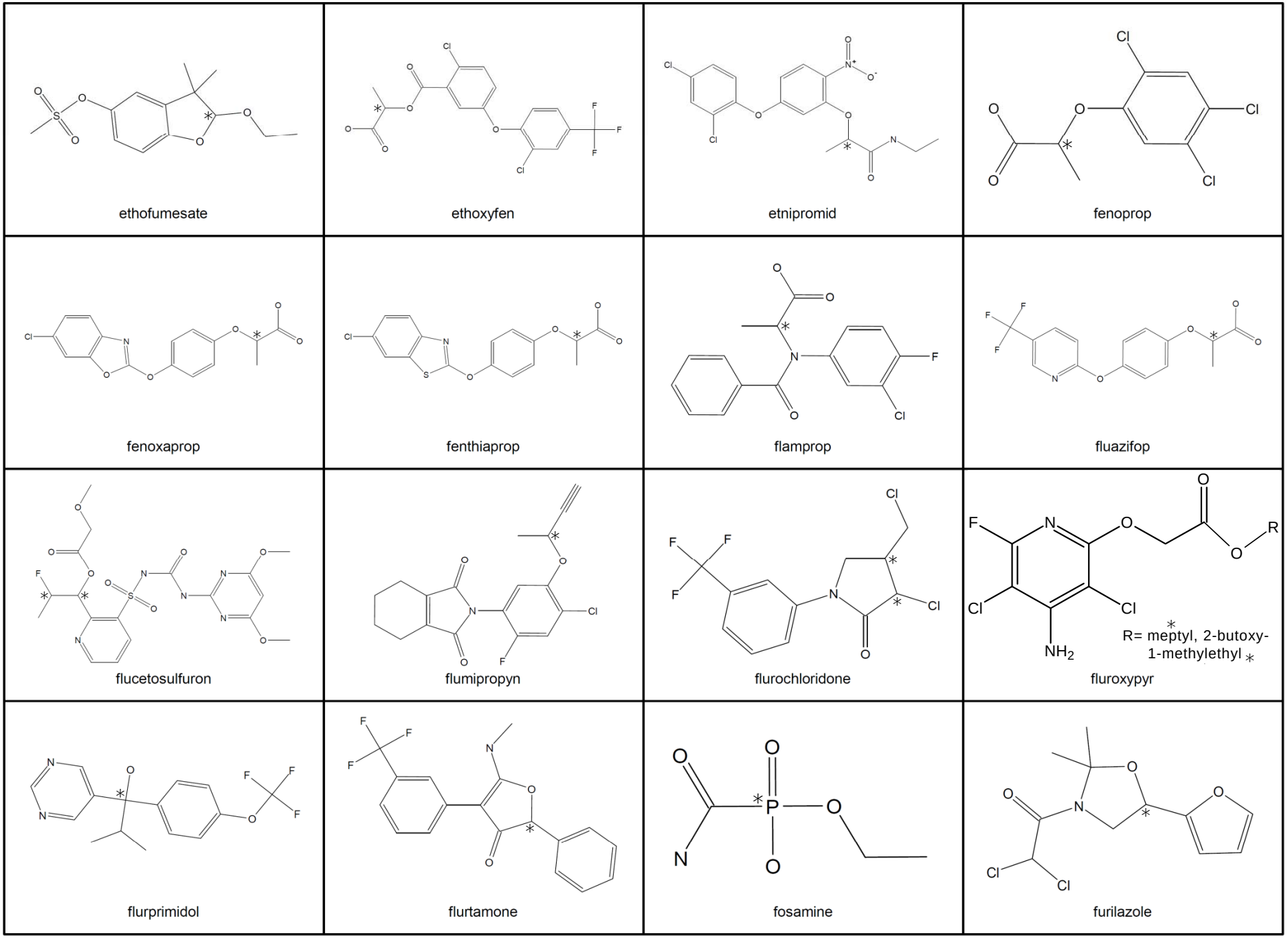
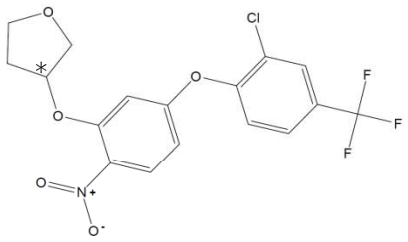

ethofumesate
ethoxyfen
etnipromid
fenoprop
fenoxaprop
fenthiaprop
flamprop
fluazifop
flucetosulfuron
flumipropyn
flurochloridone
fluroxypyr
R= meptyl, 2-butoxy-1-methylethyl
flurprimidol
flurtamone
fosamine
furilazole

Fig. 4, page 5



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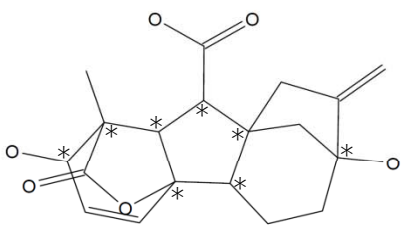

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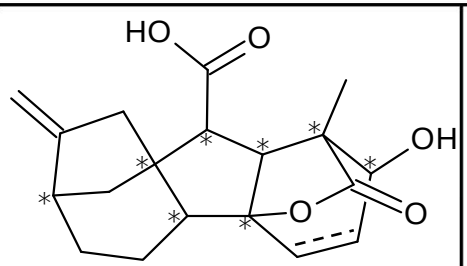
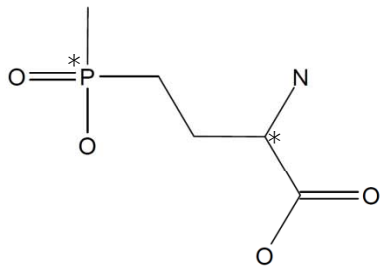


A_4: no double bond A_7:- - -

gibberellins



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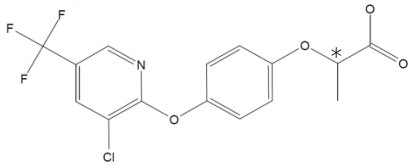

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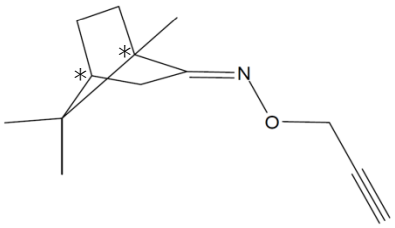

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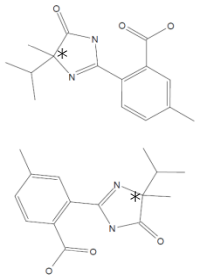

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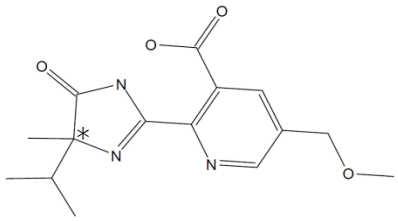

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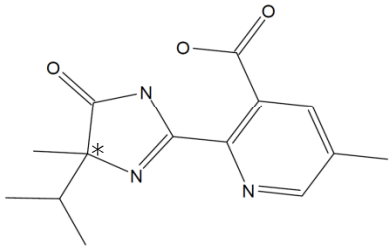

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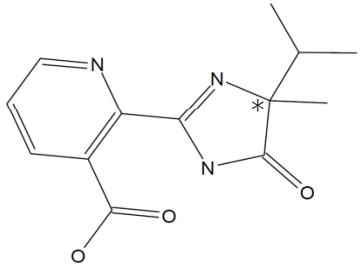

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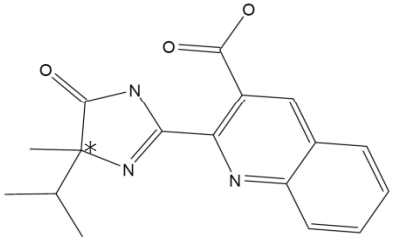

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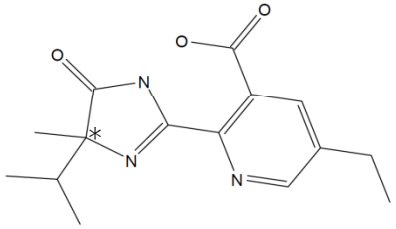

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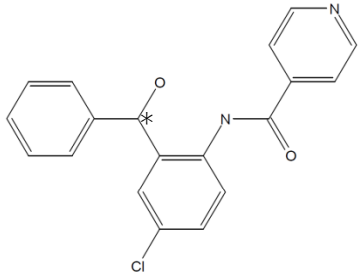

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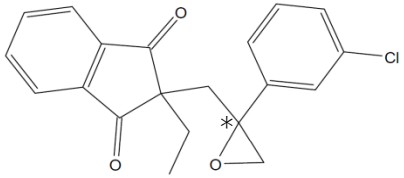

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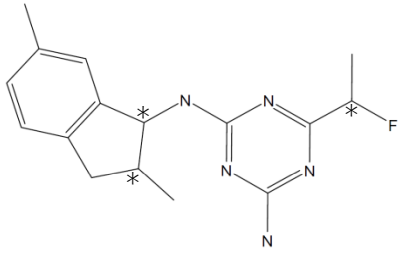

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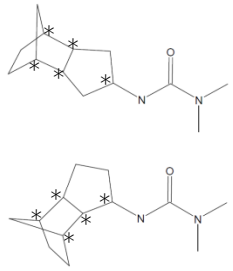

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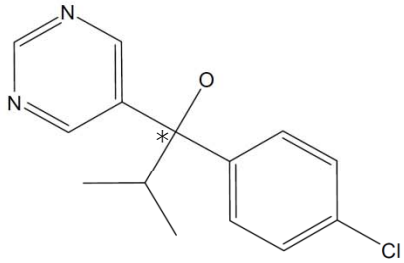
Fig. 4, page 6



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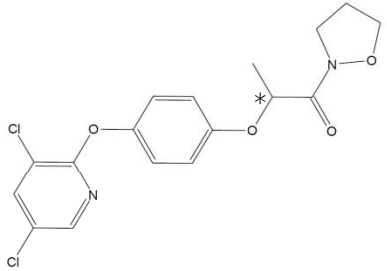

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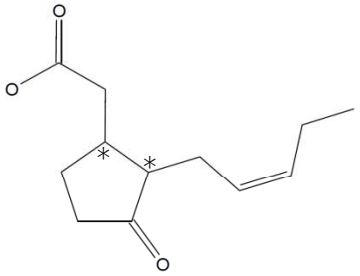

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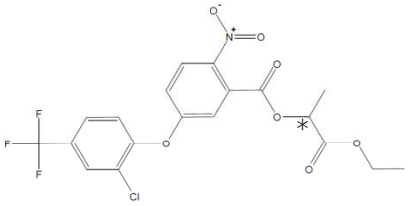

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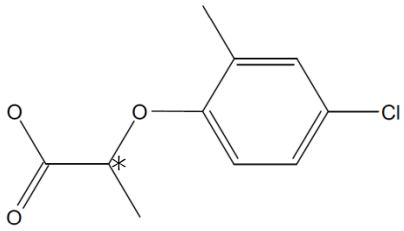

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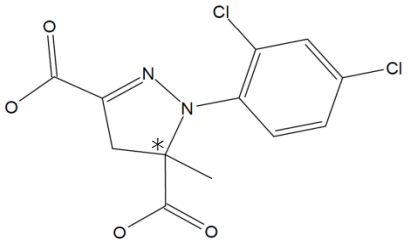

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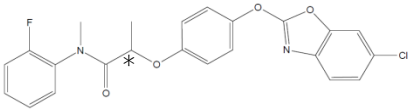

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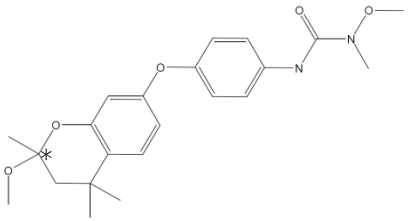

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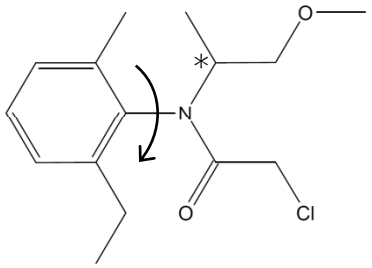

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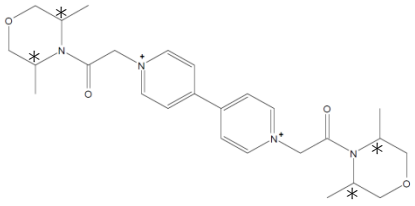

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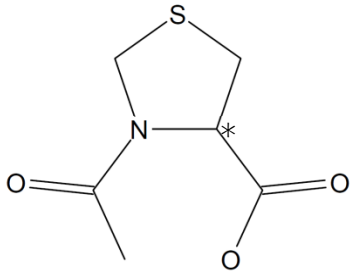
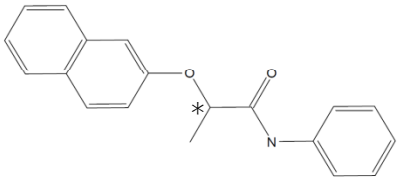
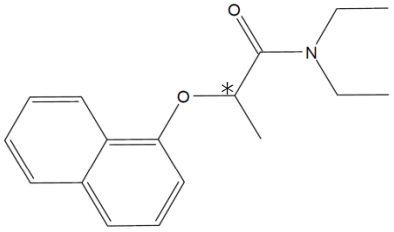


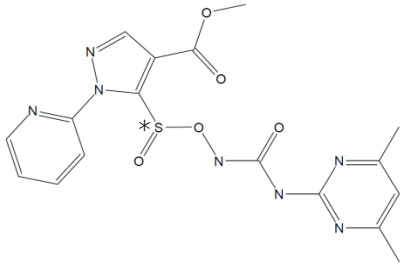
N-acetylthiazolidine-4-carboxylic acid



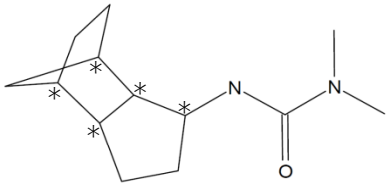
naproanilide



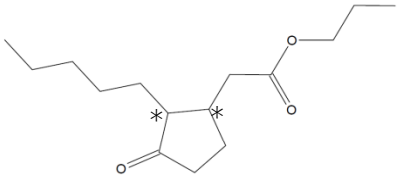
napropamide



NC-330



noruron



n-propyl dihydrojasmonate

Fig. 4, page 7

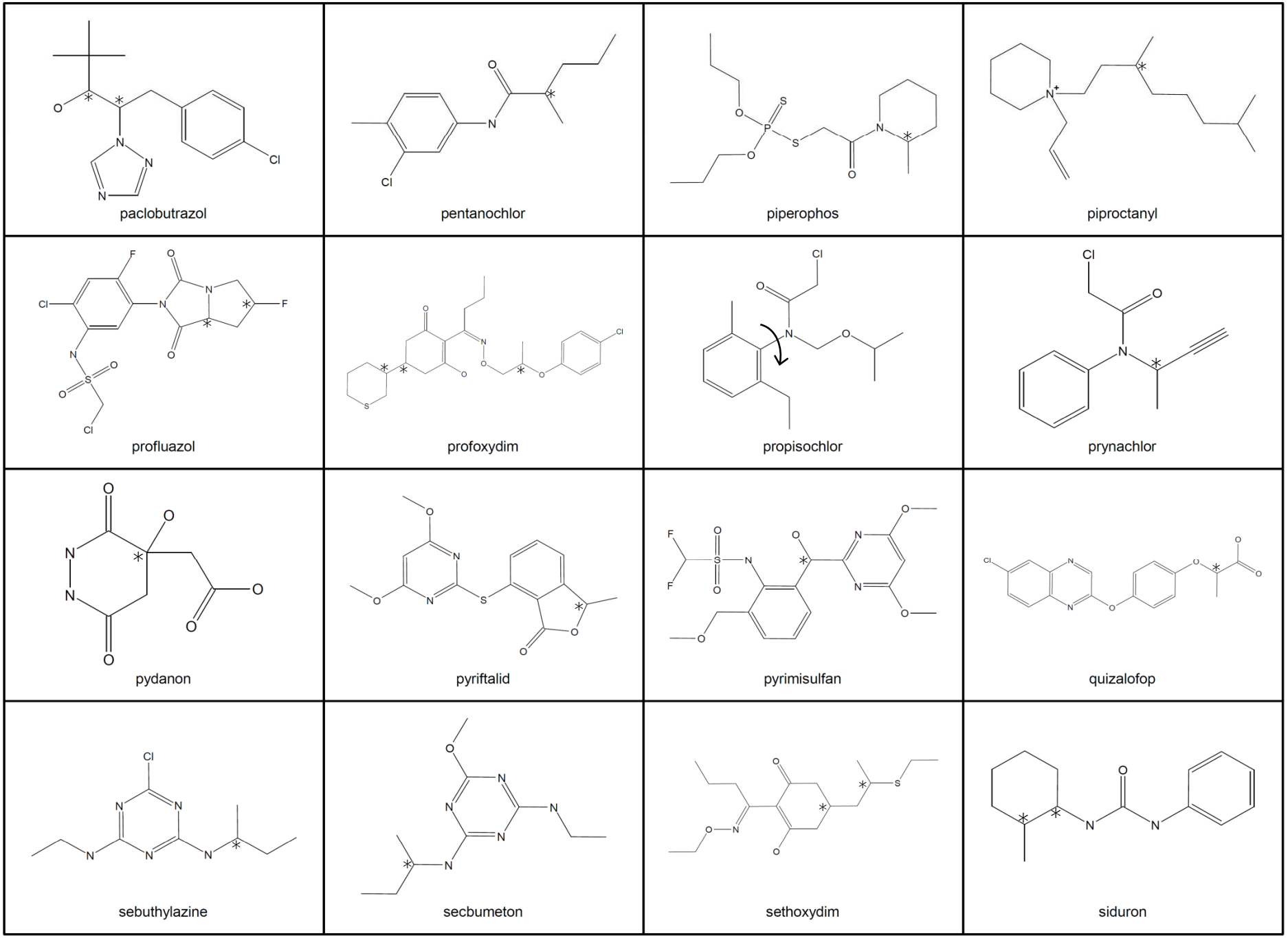
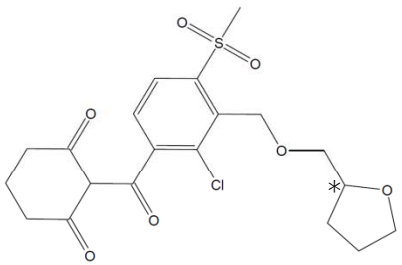
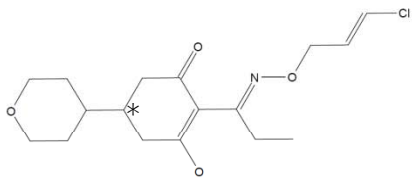

paclobutrazol
pentanochlor
piperophos
piproctanyl
profluazol
profoxydim
propisochlor
prynachlor
pydanon
pyriftalid
pyrimisulfan
quizalofop
sebuthylazine
secbumeton
sethoxydim
siduron

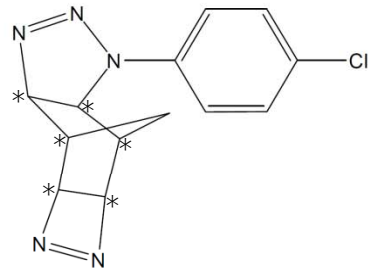
Fig. 4, page 8



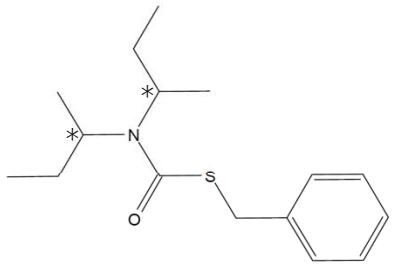
tefuryltrione



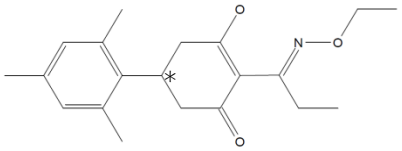
tepraloxydim



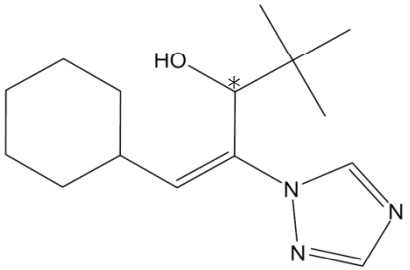
tetcyclacis



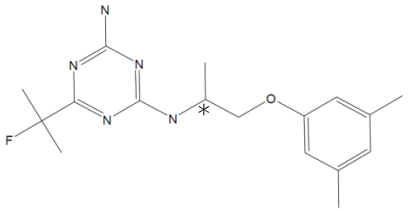
tiocarbazil



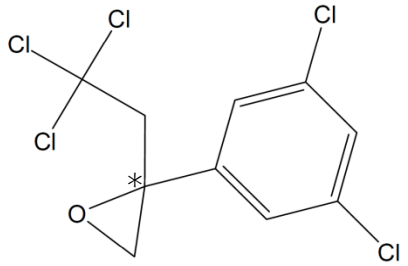
tralkoxydim



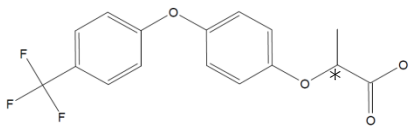
triapenthenol



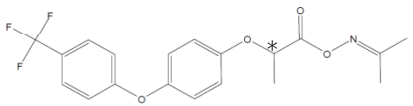
triaziflam



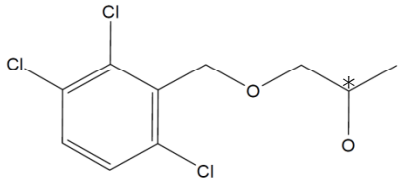
tridiphane



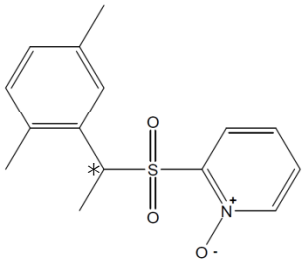
trifop



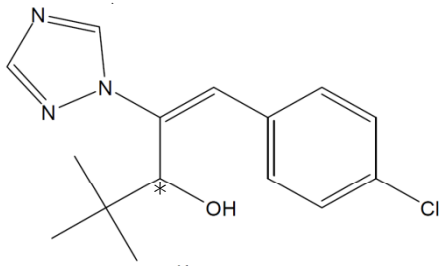
trifopsime



tritac

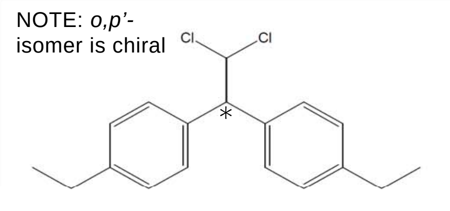


UBI-S734

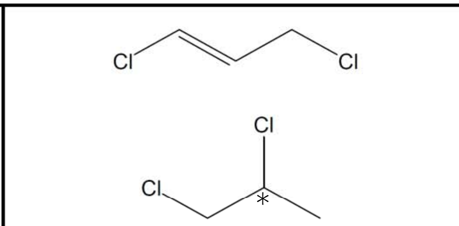


uniconazole

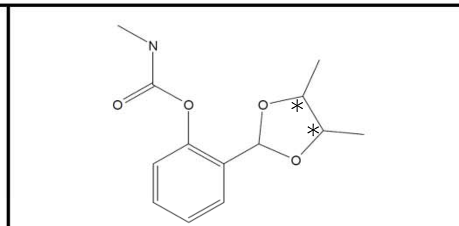
Fig. 4, page 9



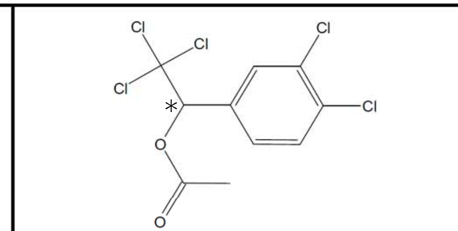
1,1-dichloro-2,2-bis(4-ethylphenyl)ethane



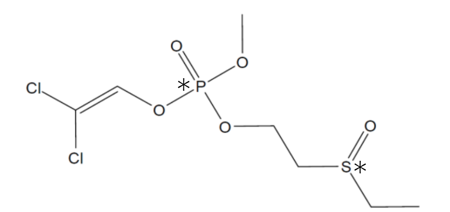
1,2-dichloropropane with 1,3-dichloropropene



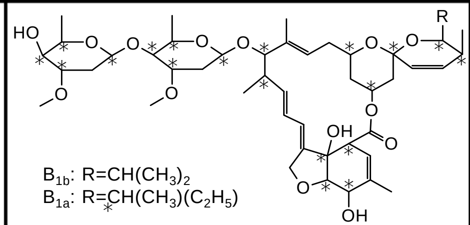
2-(4,5-dimethyl-1,3-dioxolan-2-yl)phenyl meth



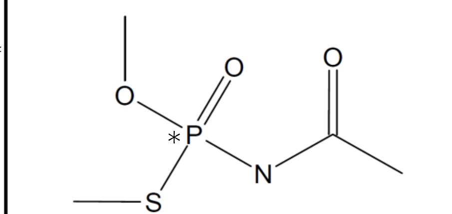
2,2,2-trichloro-1-(3,4-dichlorophenyl)ethyl ac



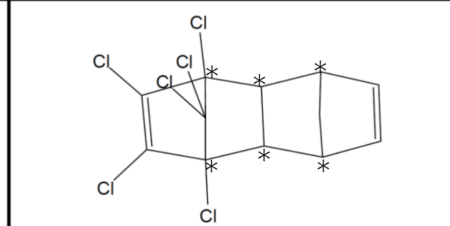
2,2-dichlorovinyl 2-ethylsulfinylethyl methyl p



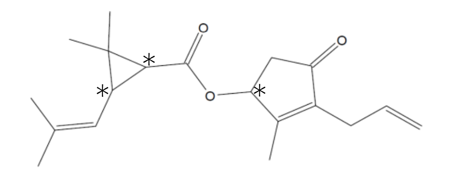
abamectin



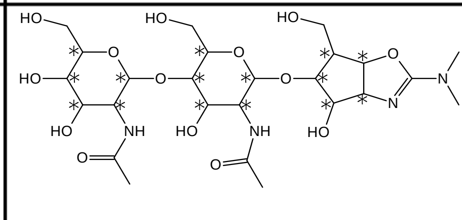
acephate



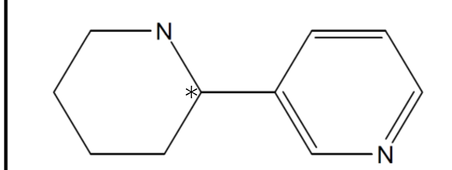
aldrin



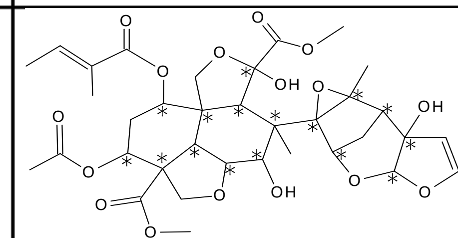
allethrin



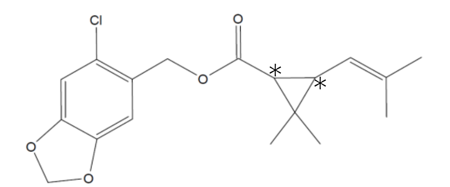
allosamidin



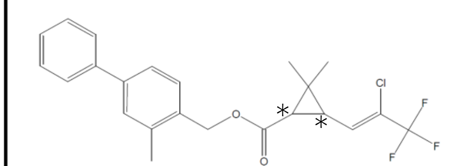
anabasine



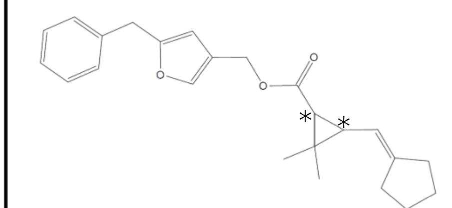
azadirachtin



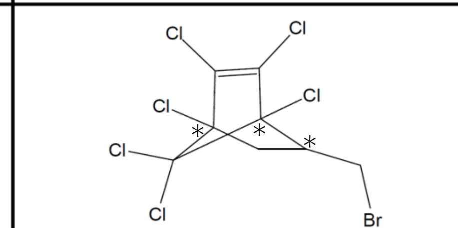
barthrin



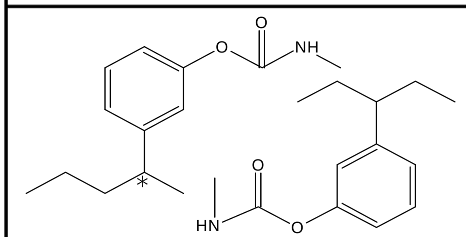
bifenthrin



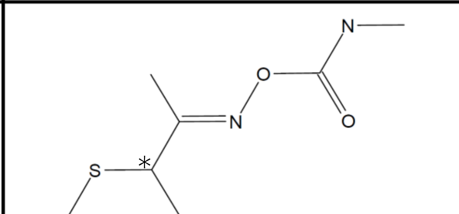
bioethanomethrin



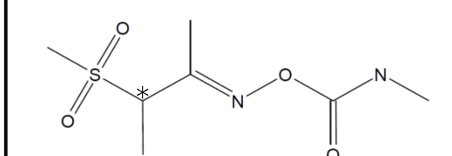
bromocyclen



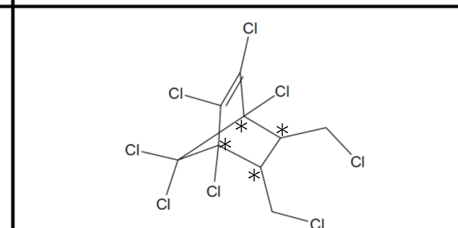
bufencarb



butocarboxim



butoxycarboxim



chlorbicyclen

Fig. 5, page 1

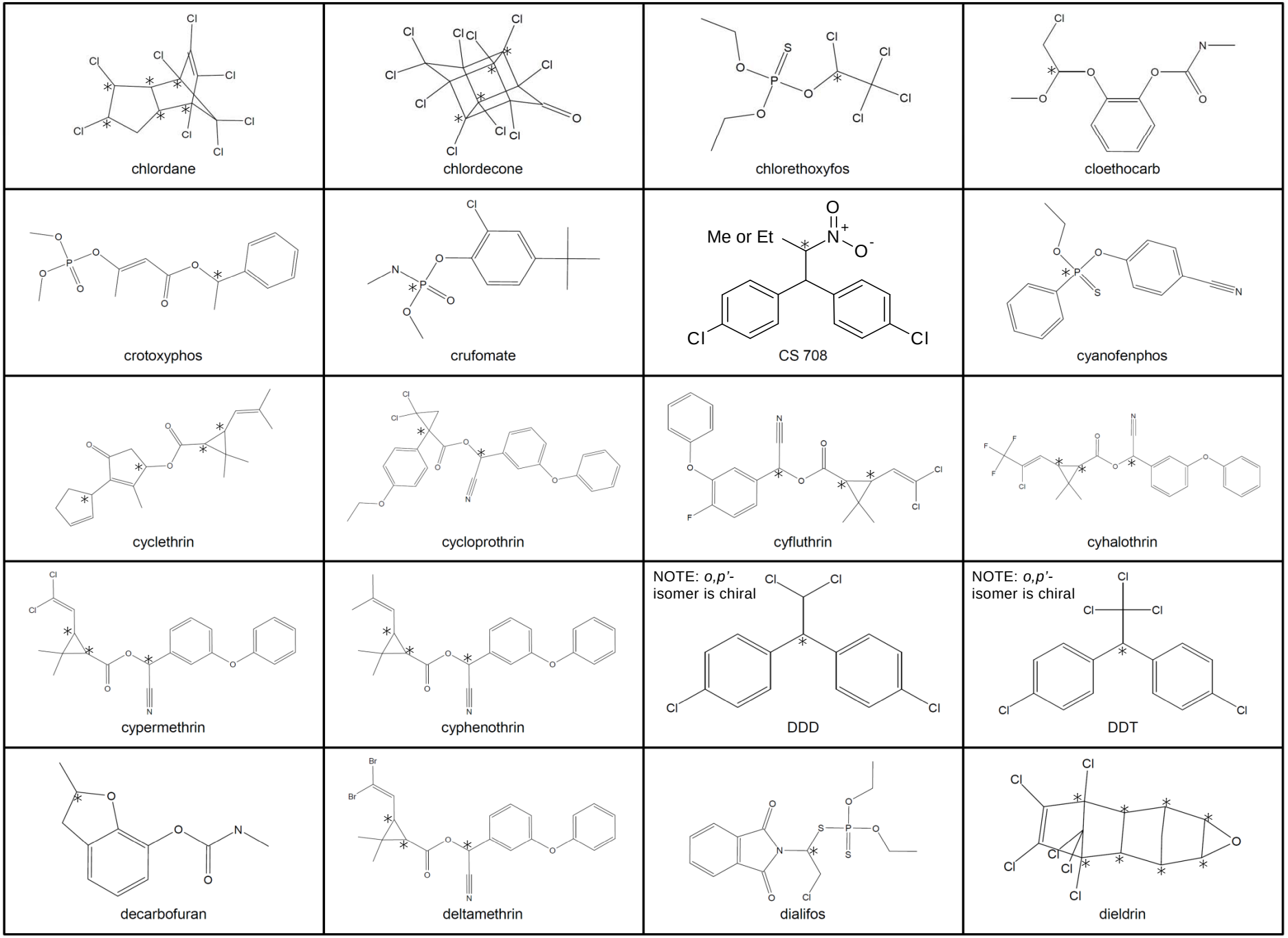

chlordane
chlordecone
chlorethoxyfos
cloethocarb
crotoxyphos
crufomate
Me or Et
CS 708
cyanofenphos
cyclethrin
cycloprothrin
cyfluthrin
cyhalothrin
cypermethrin
cyphenothrin
NOTE: o,p'-isomer is chiral
DDD
NOTE: o,p'-isomer is chiral
DDT
decarbofuran
deltamethrin
dialifos
dieldrin

Fig. 5, page 2

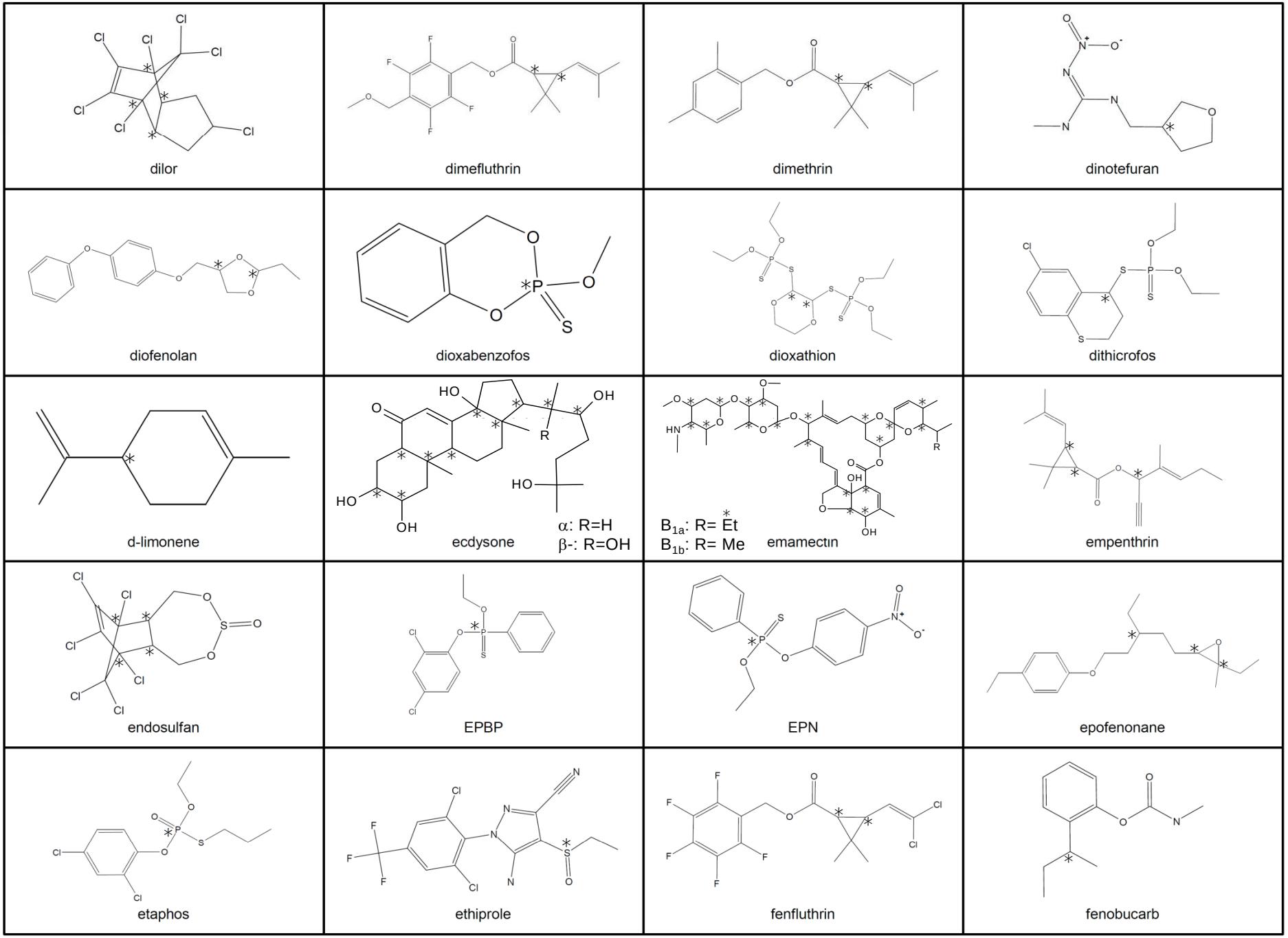

dilor
dimefluthrin
dimethrin
dinotefuran
diofenolan
dioxabenzofos
dioxathion
dithicrofos
d-limonene
ecdysone
α: R=H
β-: R=OH
B1a: R= Et
B1b: R= Me
emamectin
empenthrin
endosulfan
EPBP
EPN
epofenonane
etaphos
ethiprole
fenfluthrin
fenobucarb

Fig. 5, page 3

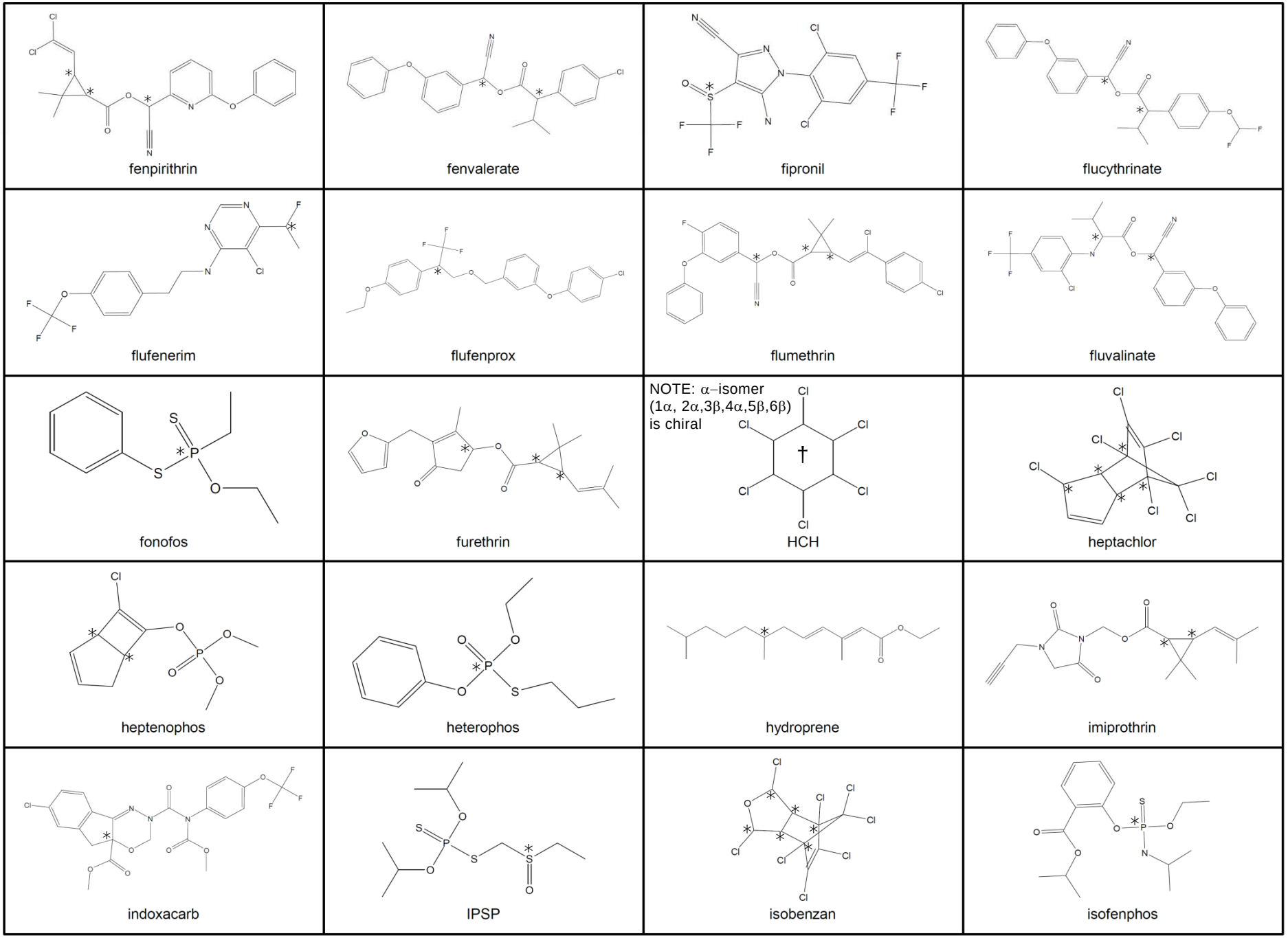
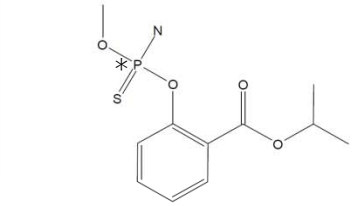
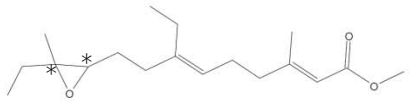

fenpirithrin
fenvalerate
fipronil
flucythrinate
flufenerim
flufenprox
flumethrin
fluvalinate
fonofos
furethrin
NOTE: α–isomer
(1α, 2α,3β,4α,5β,6β)
is chiral
HCH
heptachlor
heptenophos
heterophos
hydroprene
imiprothrin
indoxacarb
IPSP
isobenzan
isofenphos

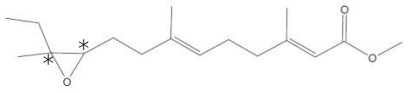
Fig. 5, page 4



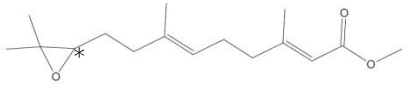
isopropyl O-(methoxyaminothiophosphoryl)sa



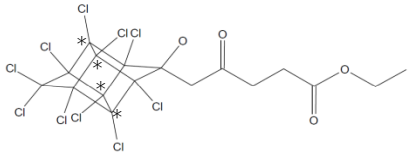
juvenile hormone I



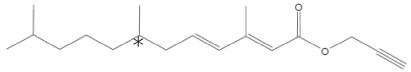
juvenile hormone II



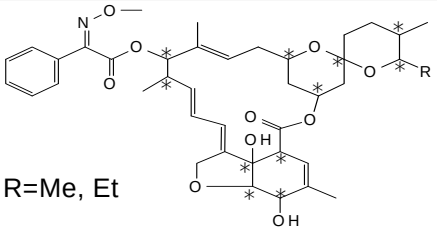
juvenile hormone III



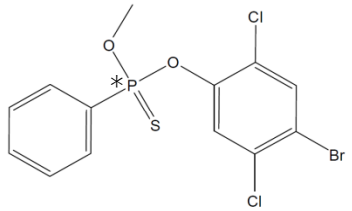
kelevan



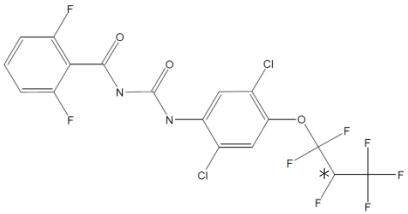
kinoprene



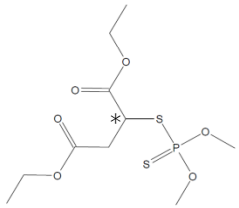
lepimectin



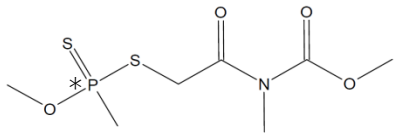
leptophos



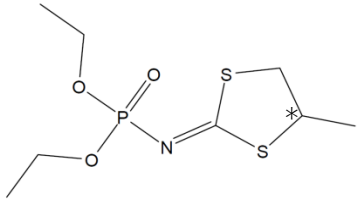
lufenuron



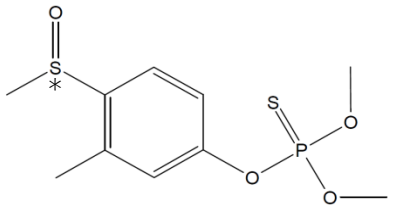
malathion



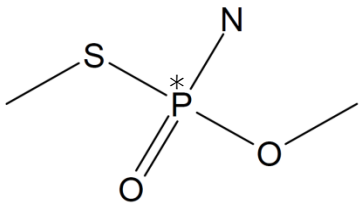
mecarphon



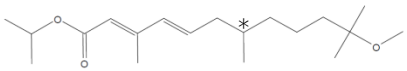
mephosfolan



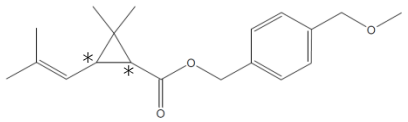
mesulfenfos



methamidophos

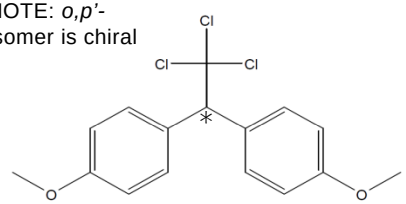


methoprene

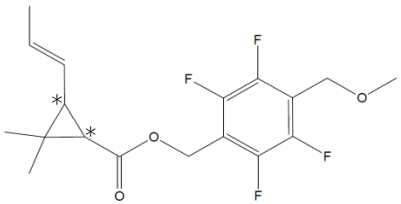


methothrin

NOTE: *o,p'*-
isomer is chiral



methoxychlor



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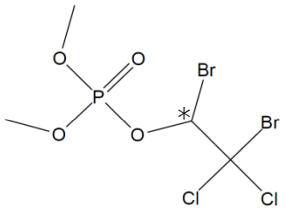
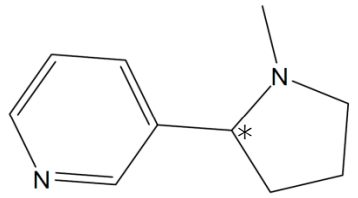
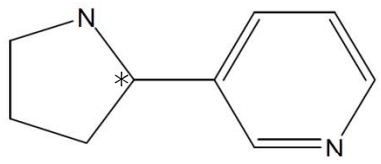


naled

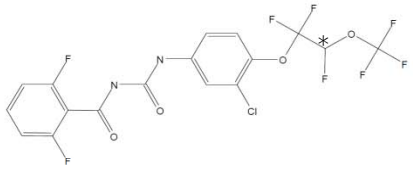


nicotine

Fig. 5, page 5



nornicotine



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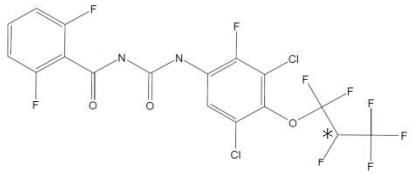

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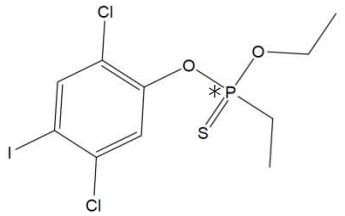
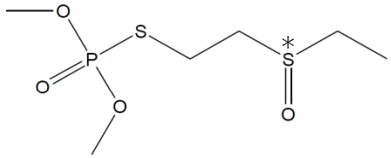
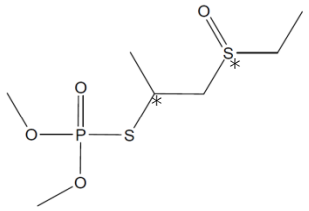


O-2,5-dichloro-4-iodophenyl O-ethyl ethylpho



oxydemeton-methyl



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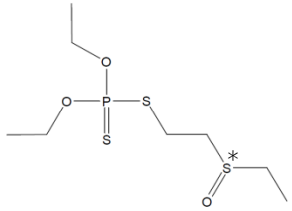
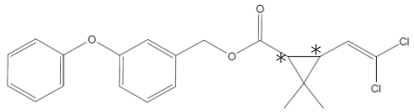
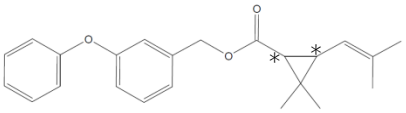


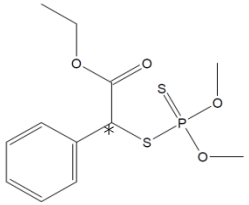
oxydisulfoton



permethrin



phenothrin



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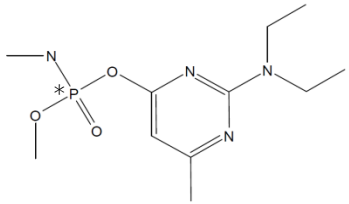
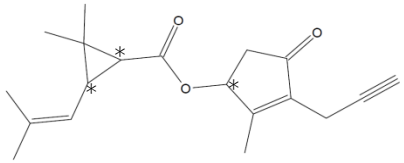
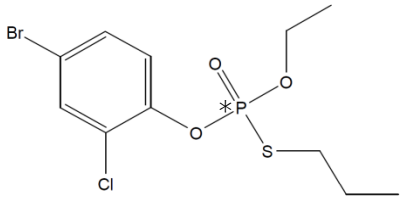


pirimetaphos



prallethrin



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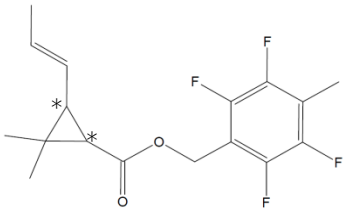
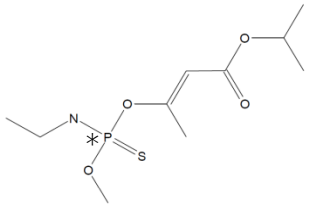


profluthrin



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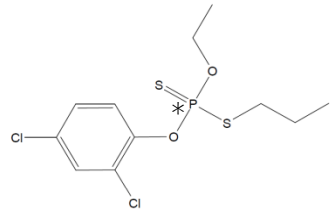

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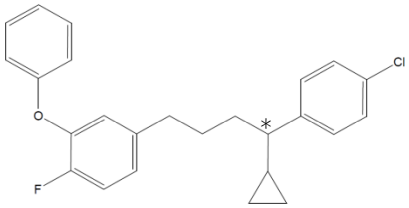
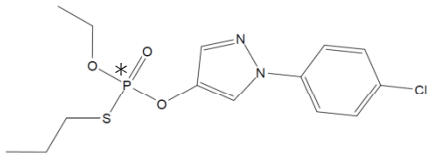
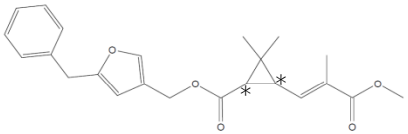


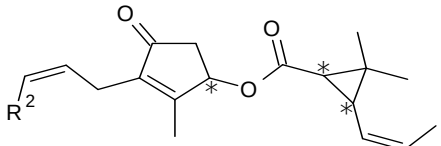
protrifenbute



pyraclofos



pyresmethrin



cinerin: R^2= Me; jasmolin: R^2= Et
pyrethrin R^2= $CH{=}CH_2$
I: R^1= Me; II: R^1= CO_2CH_3

pyrethrins

Fig. 5, page 6

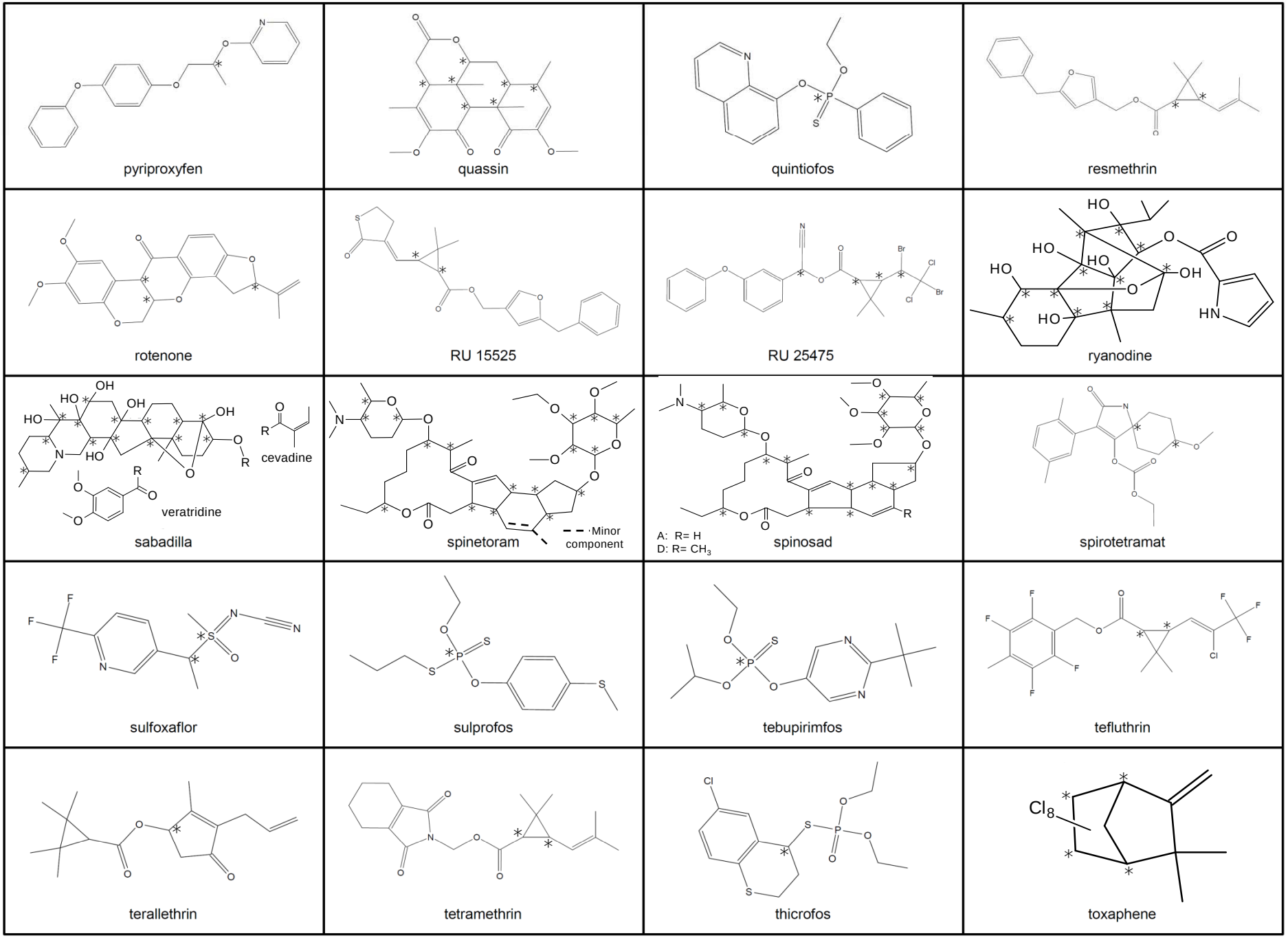
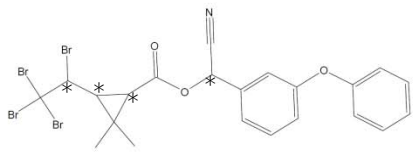
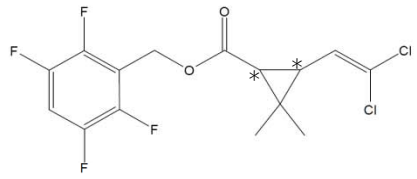

pyriproxyfen
quassin
quintiofos
resmethrin
rotenone
RU 15525
RU 25475
ryanodine
cevadine
veratridine
sabadilla
spinetoram
Minor component
A: R= H
D: R= CH3
spinosad
spirotetramat
sulfoxaflor
sulprofos
tebupirimfos
tefluthrin
terallethrin
tetramethrin
thicrofos
toxaphene

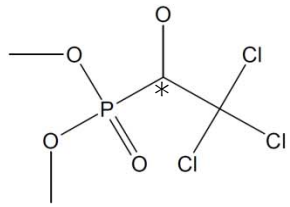
Fig. 5, page 7



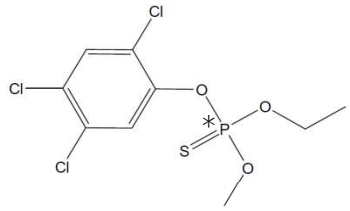
tralomethrin



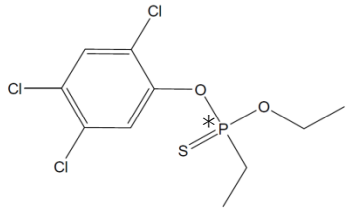
transfluthrin



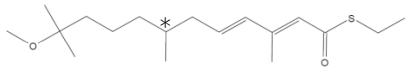
trichlorfon



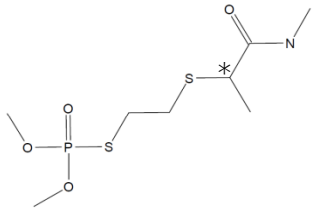
trichlormetaphos-3



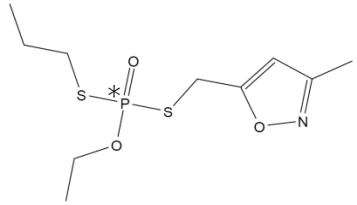
trichloronat



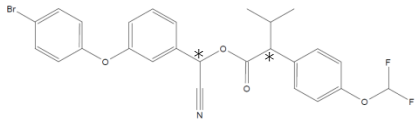
triprene



vamidothion

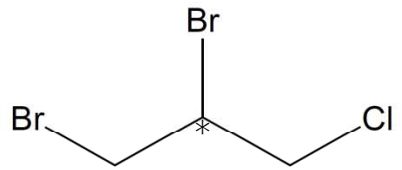


zolaprofos

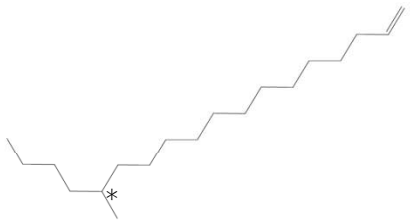


ZXI 8901

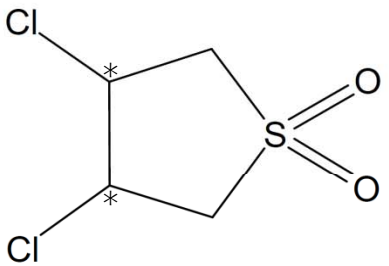
Fig. 5, page 8



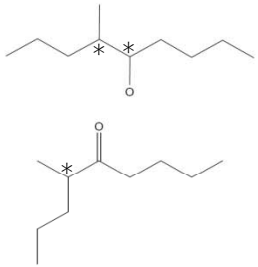
1,2-dibromo-3-chloropropane



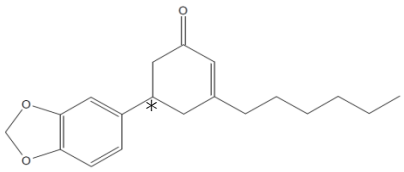
14-methyloctadecene



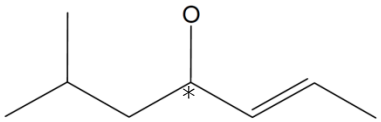
3,4-dichlorotetrahydrothiophene 1,1-dioxide



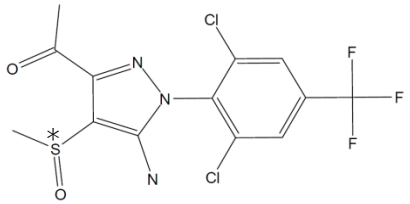
4-methylnonan-5-ol w/ 4-methylnonan-5-one



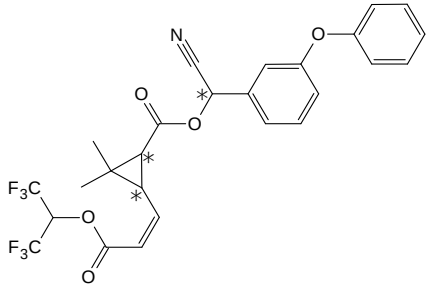
5-(1,3-benzodioxol-5-yl)-3-hexylcyclohex-2-e



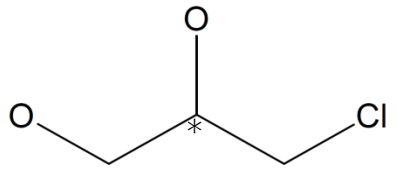
6-methylhept-2-en-4-ol



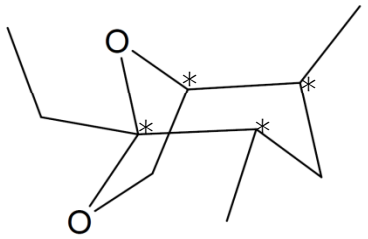
acetoprole



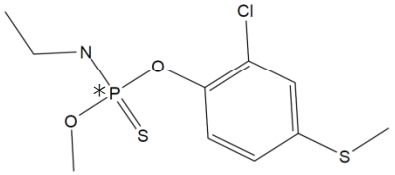
acrinathrin



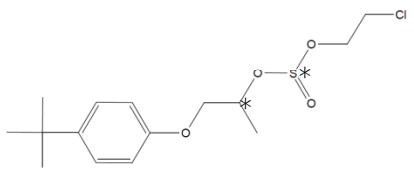
alpha-chlorohydrin



alpha-multistriatin



amidothioate



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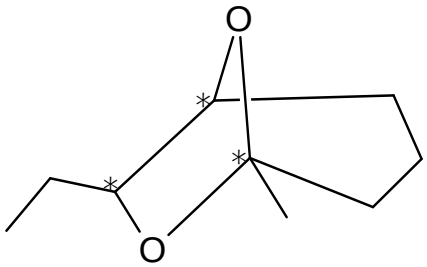
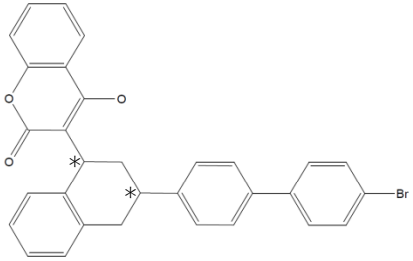
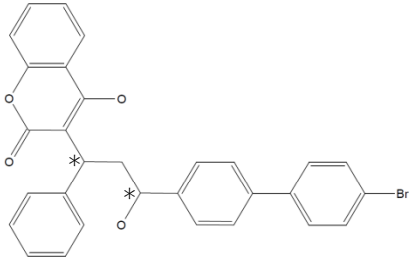


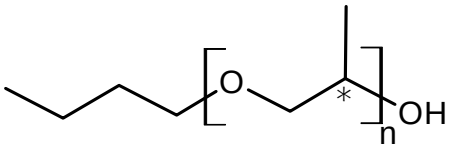
brevicomin



brodifacoum

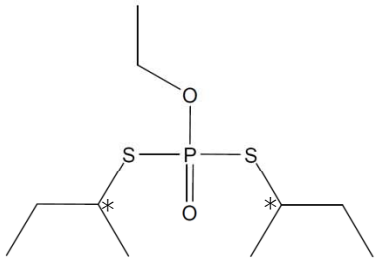


bromadiolone

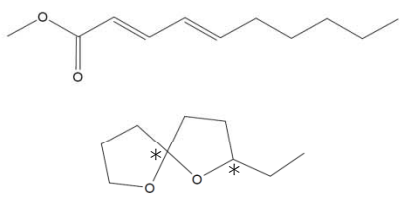


butoxy(polypropylene glycol)

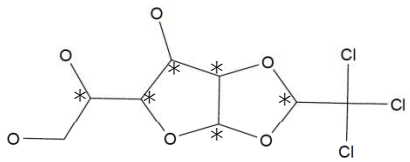
Fig. 6, page 1



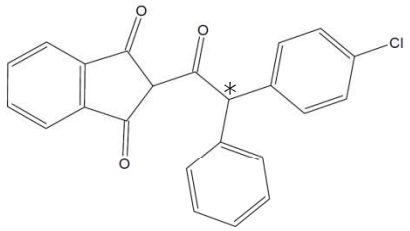
cadusafos



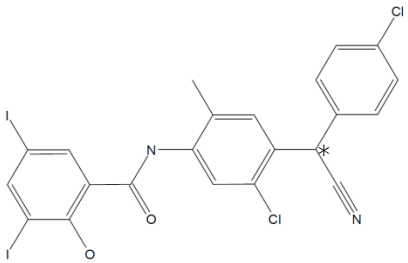
chalcogran with methyl decadienoate



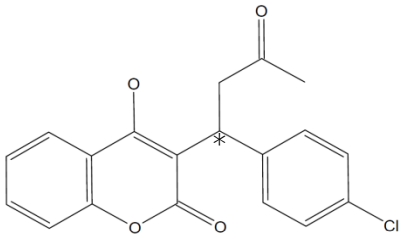
chloralose



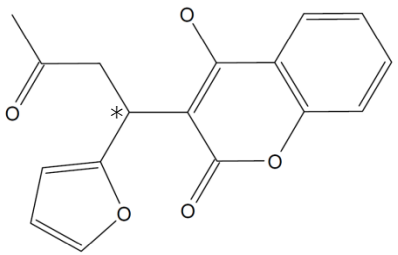
chlorophacinone



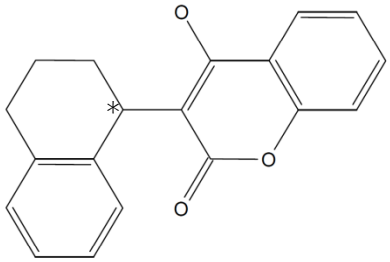
closantel



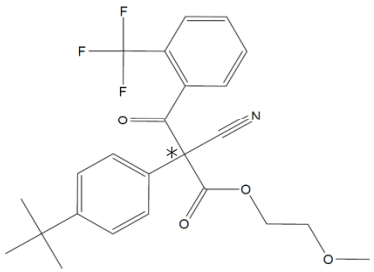
coumachlor



coumafuryl



coumatetralyl



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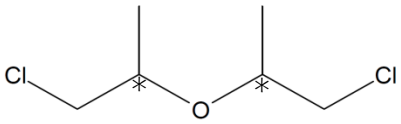
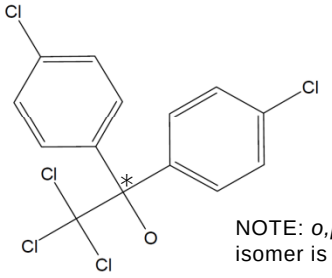
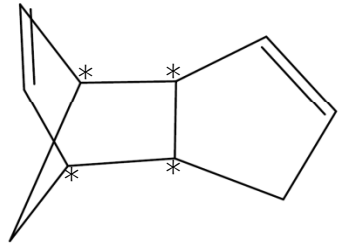


DCIP

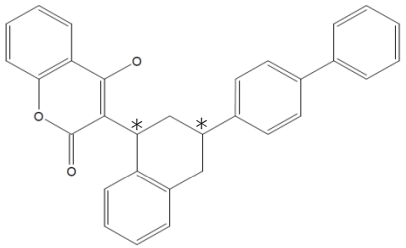


NOTE: *o,p'*-isomer is chiral

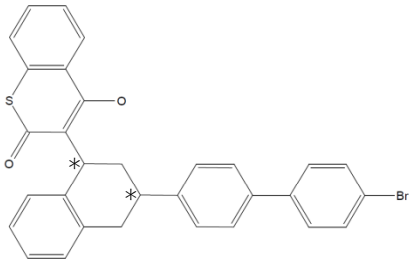
dicofol



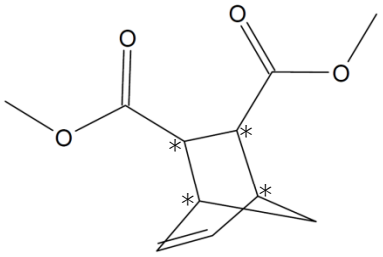
dicyclopentadiene



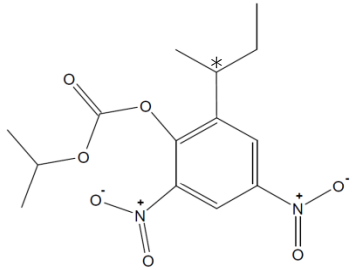
difenacoum



difethialone

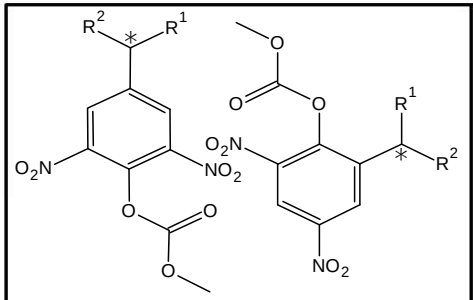


dimethyl carbate



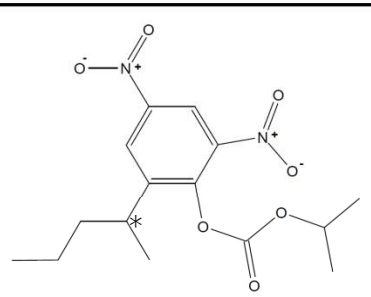
dinobuton

Fig. 6, page 2

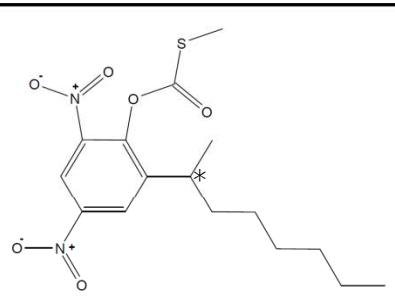


dinocton

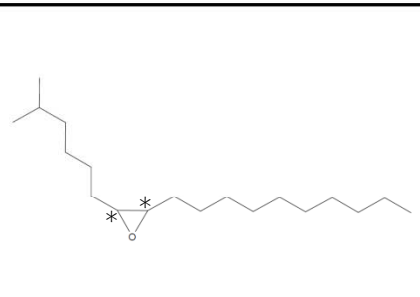
R^1= Et, R^2= Pe or R^1= Pr, R^2= Bu



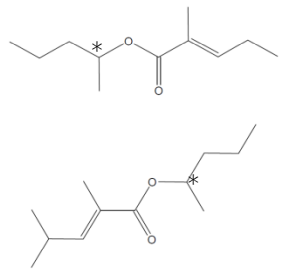
dinopenton



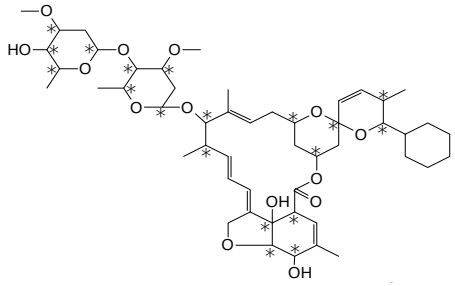
dinosulfon



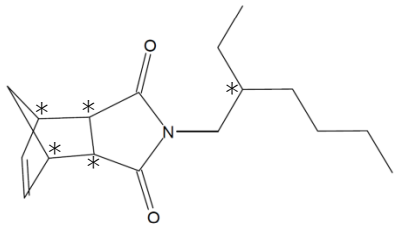
disparlure



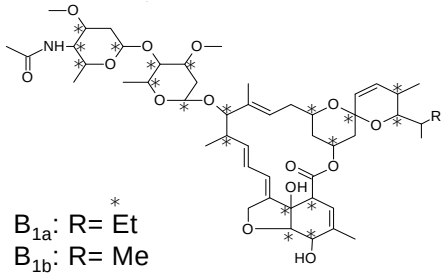
dominicalure



doramectin



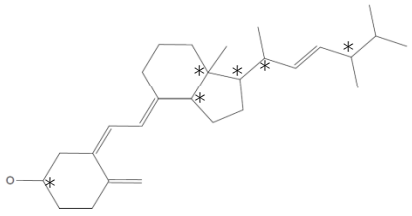
ENT 8184



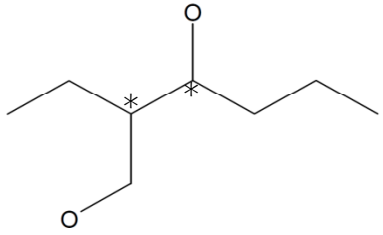
B_{1a}: R= Et

B_{1b}: R= Me

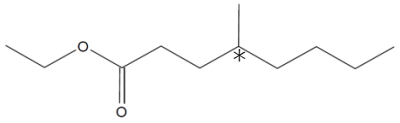
eprinomectin



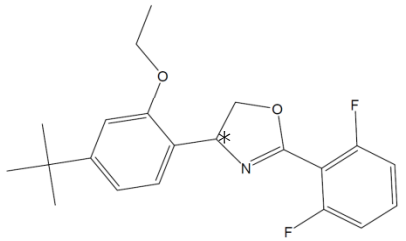
ergocalciferol



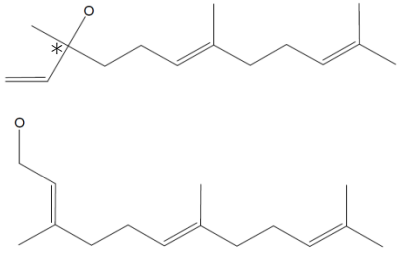
ethohexadiol



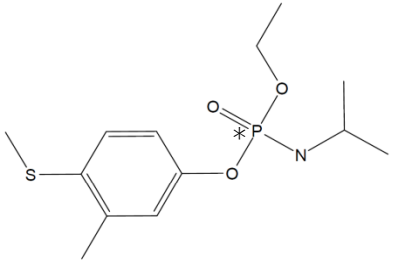
ethyl 4-methyloctanoate



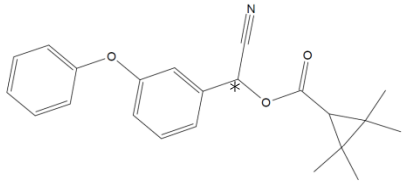
etoxazole



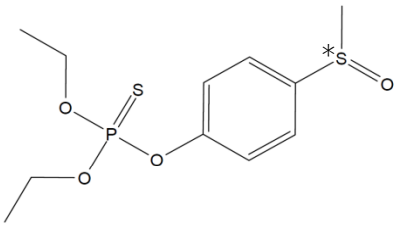
farnesol with nerolidol



fenamiphos



fenpropathrin



fensulfothion

Fig. 6, page 3

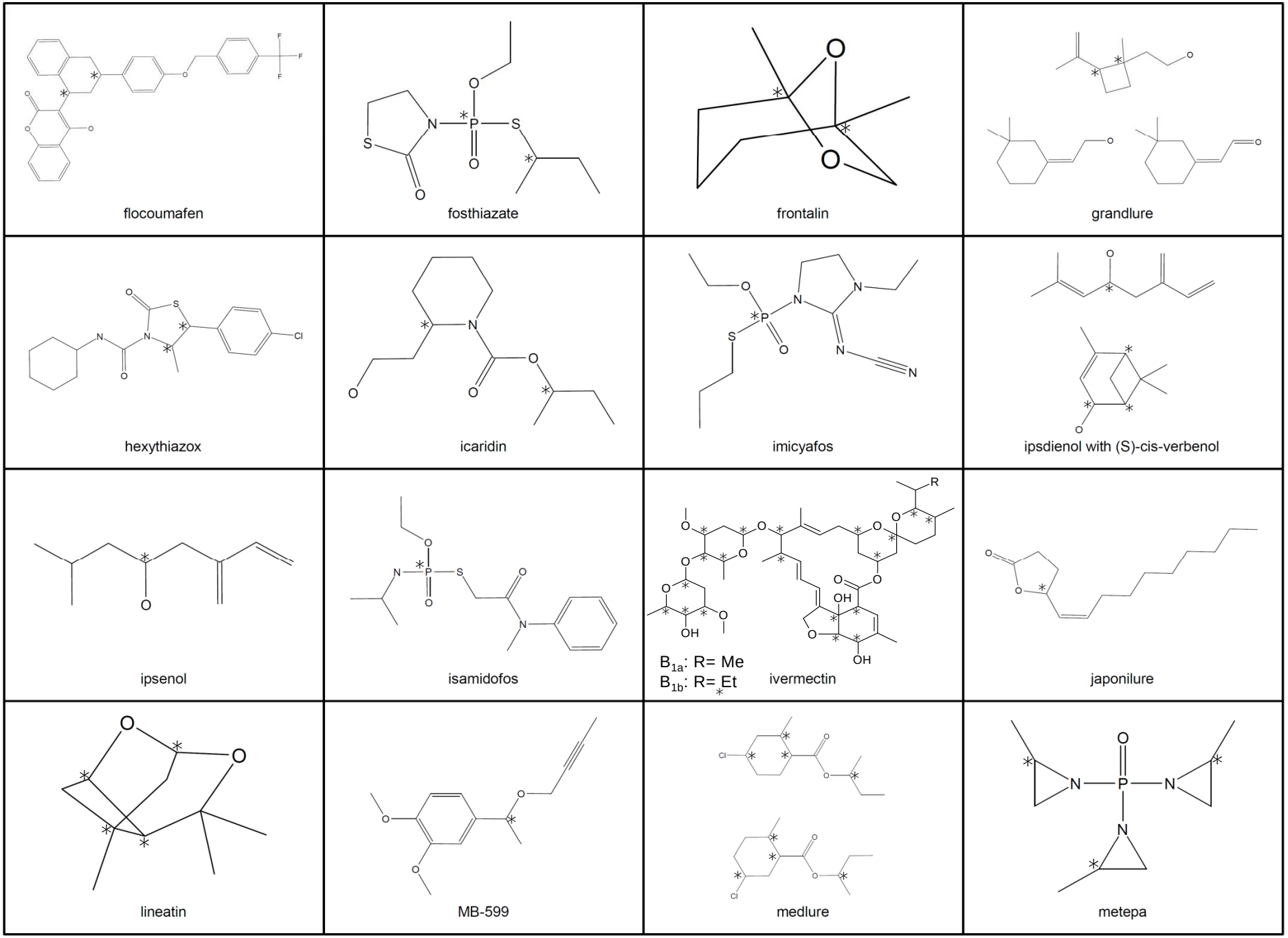

flocoumafen
fosthiazate
frontalin
grandlure
hexythiazox
icaridin
imicyafos
ipsdienol with (S)-cis-verbenol
ipsenol
isamidofos
B_{1a}: R= Me
B_{1b}: R= Et
ivermectin
japonilure
lineatin
MB-599
medlure
metepa

Fig. 6, page 4

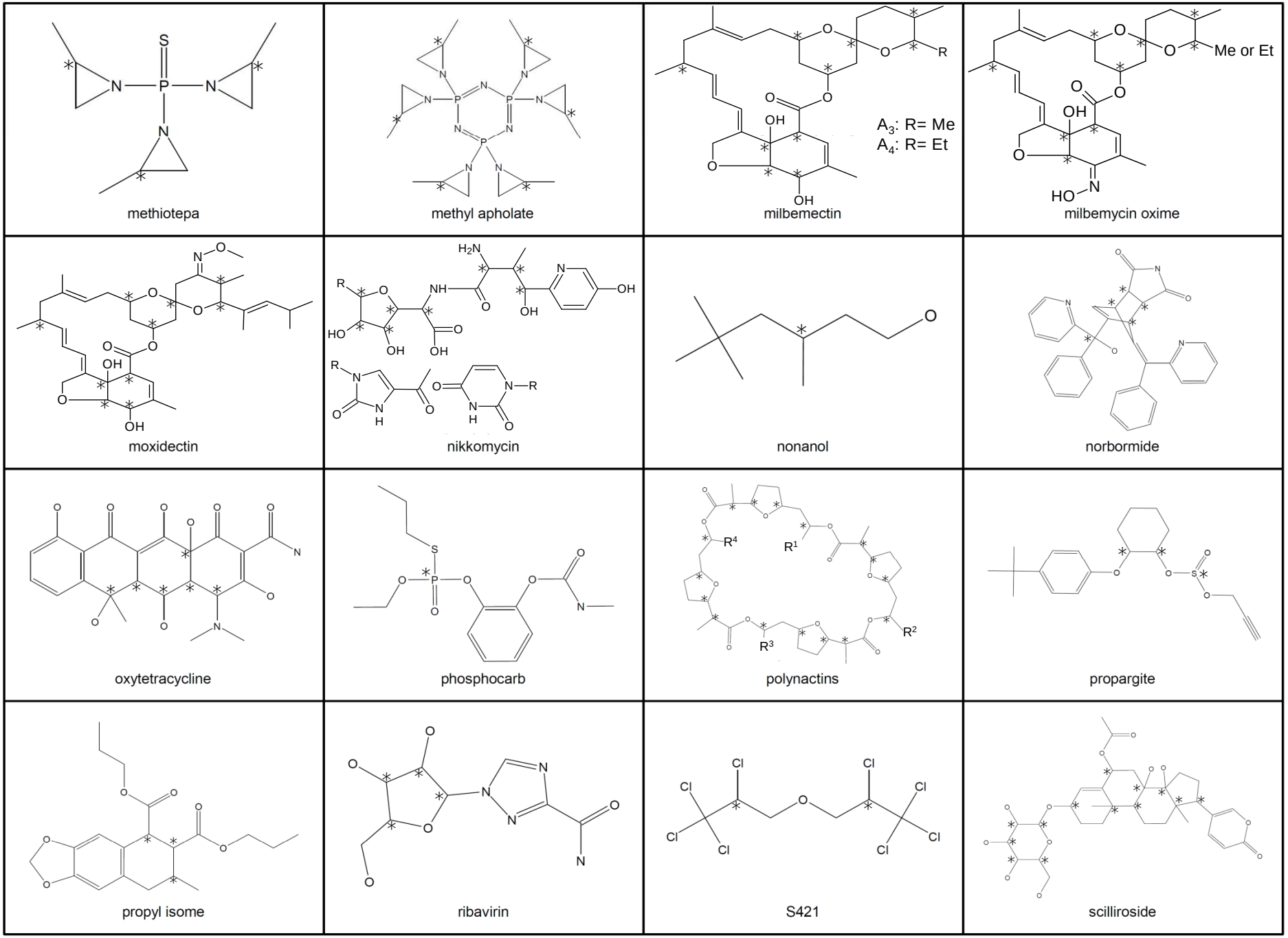
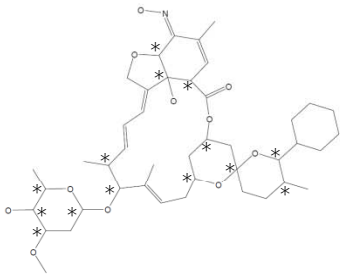
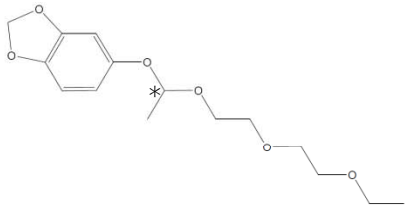

methiotepa
methyl apholate
milbemectin
A3: R= Me
A4: R= Et
milbemycin oxime
Me or Et
moxidectin
nikkomycin
nonanol
norbormide
oxytetracycline
phosphocarb
polynactins
propargite
propyl isome
ribavirin
S421
scilliroside

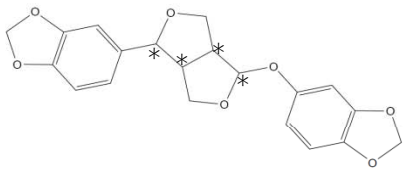
Fig. 6, page 5



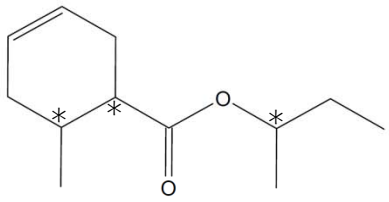
selamectin



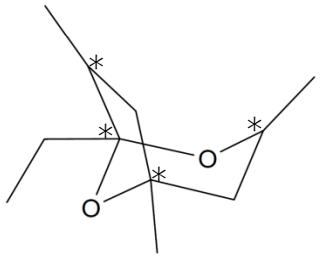
sesamex



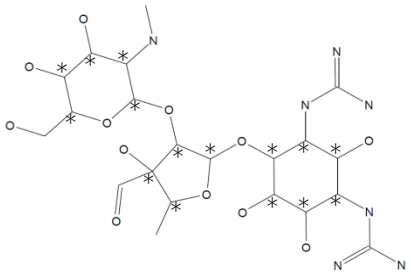
sesamolin



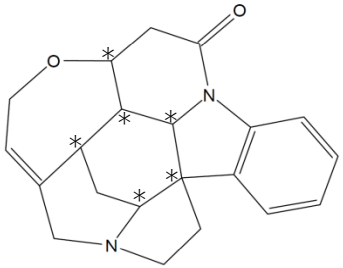
siglure



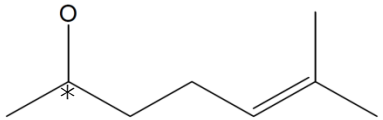
sordidin



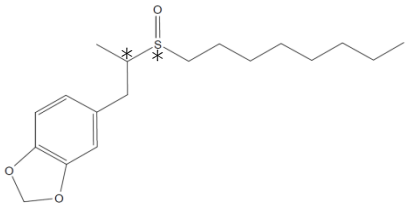
streptomycin



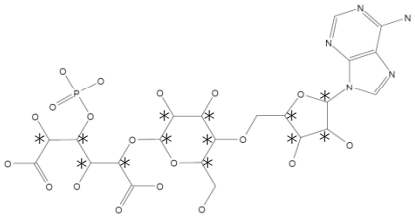
strychnine



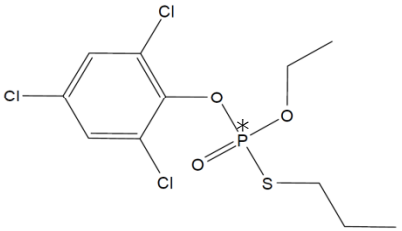
sulcatol



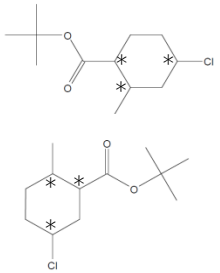
sulfoxide



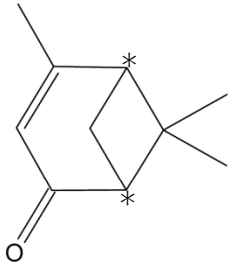
thuringiensin



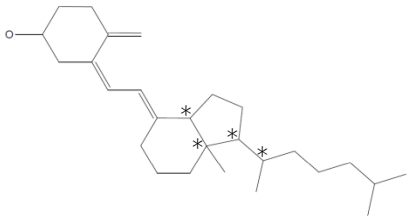
trifenofos



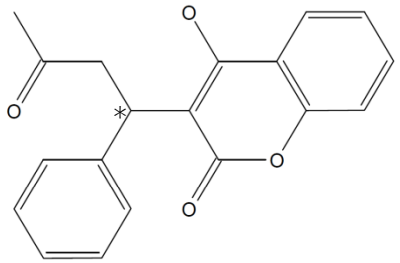
trimedlure



verbenone



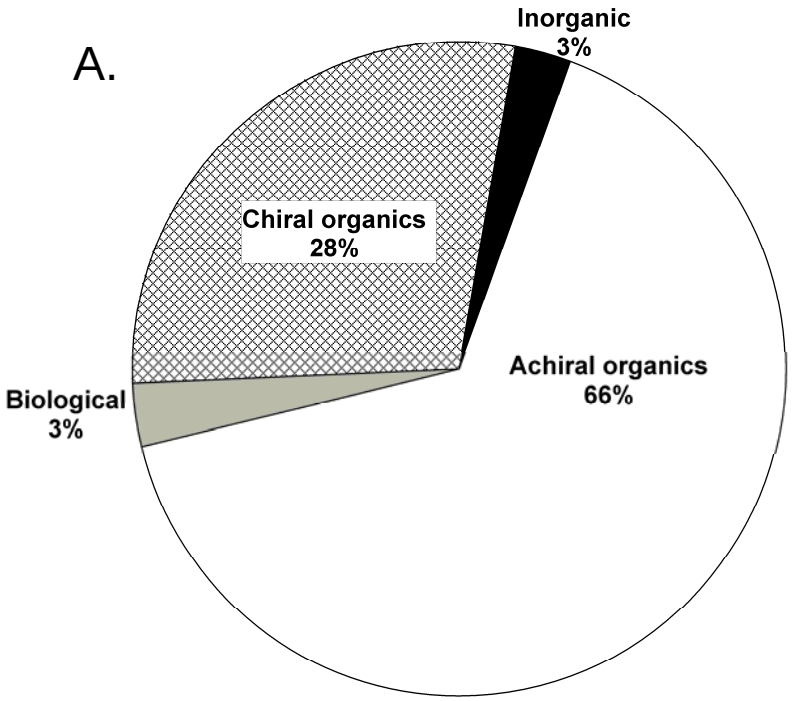
vitamin D3



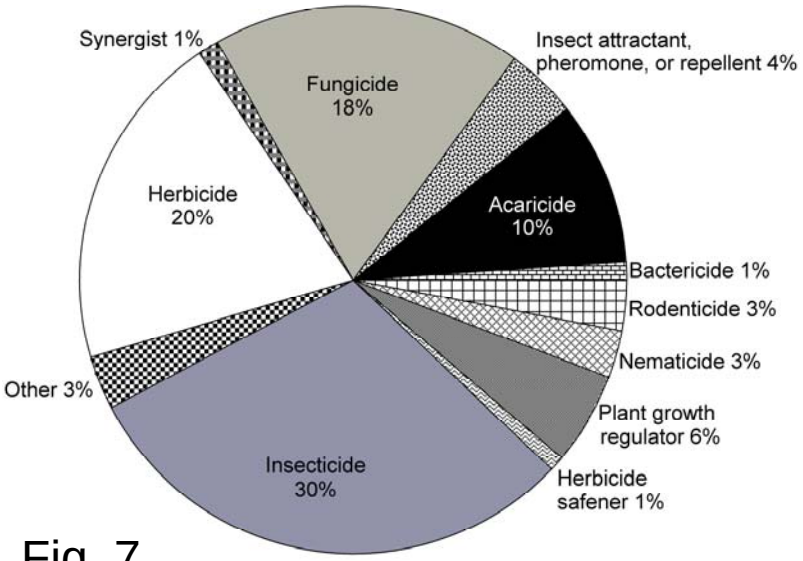
warfarin

Fig. 6, page 6

A.


Inorganic
3%
Chiral organics
28%
Achiral organics
66%
Biological
3%

B.


Synergist 1%
Insect attractant,
pheromone, or repellent 4%
Fungicide
18%
Herbicide
20%
Acaricide
10%
Bactericide 1%
Rodenticide 3%
Nematicide 3%
Other 3%
Plant growth
regulator 6%
Insecticide
30%
Herbicide
safener 1%

C.

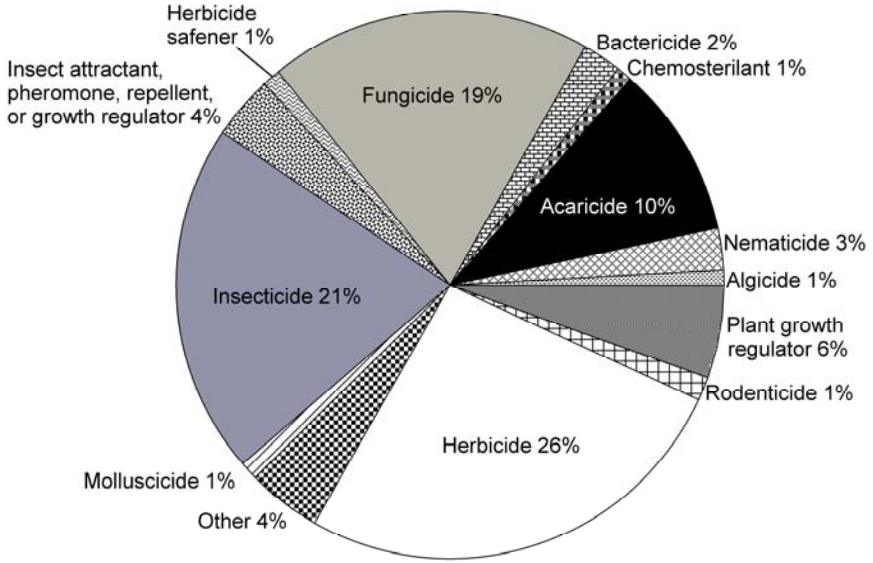

Herbicide
safener 1%
Bactericide 2%
Chemosterilant 1%
Insect attractant,
pheromone, repellent,
or growth regulator 4%
Fungicide 19%
Acaricide 10%
Nematicide 3%
Algicide 1%
Insecticide 21%
Plant growth
regulator 6%
Rodenticide 1%
Herbicide 26%
Molluscicide 1%
Other 4%

Fig. 7