Chapter

Biomimetic and Hemisynthetic Pesticides

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Abstract

Pests are responsible for most losses associated with agricultural crops. In addition, due to the indiscriminate use of synthetic pesticides, several problems have arisen over the years, such as pest resistance and contamination of important planetary sources such as water, air and soil. This awareness regarding pest problems and environment has led to the search for powerful and eco-friendly pesticides that degrade after some time, avoiding pest persistence resistance, which is also pest-specific, non-phytotoxic, nontoxic to mammals, and relatively less expensive in order to obtain a sustainable crop production Biodegradable biomimetic pesticides can be a potential green alternative to the pest industry.

Keywords: biopesticides, biomimetic, phytochemistry

1. Introduction

Chlordecone (CLD, **Figure 1**), a chlorinated insecticide, with a homocubane structure was used in Guadeloupe and Martinique (French West Indies (FWI)) to control the banana weevil, *Cosmopolites sordidus* from 1971 to 1993. Larvae of this insect are the most destructive stage, and they use their strong mandibles to escavate and create tunnels or galleries in the rhizome of banana trees [1]. To fight against this insect in the FWI, CLD was marketed in France from 1981 to 1993 as a formulation called Curlone®. The authorization for CLD was withdrawn by the French Ministry of Agriculture in 1990 but used in the FWI until September 1993. The estimated chlordecone amount applied over this time is 300 tons [2]. CLD is a very stable compound due to its high persistence; consequently, the entire environment (soil, surface, ground water and costal marine waters) and food chain remain contaminated. Therefore, animals, raised in banana production areas, are affected by this molecule [3, 4].

In banana cultivated areas of Guadeloupe, CLD concentrations between 0.1 and 37.4 $mg.kg^{-1}$ can be found in topsoil and up to 10 $\mu g.L^{-1}$ in aquatic systems [5]. Following the contamination of foodstuffs, the population of Guadeloupe and Martinique is exposed to chlordecone contamination through the consumption of

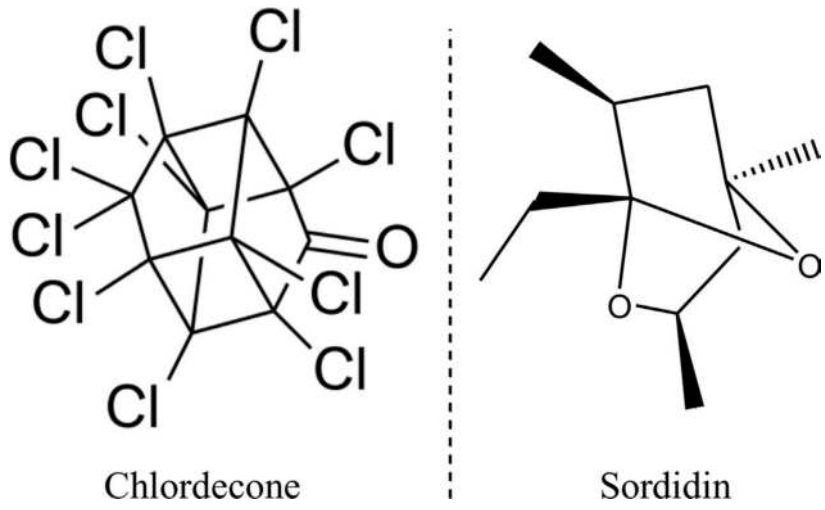


Figure 1.
Chlordecone (left) and sordidin (right) structures.

contaminated food and drinking water [6]. As a consequence, 92.5% of Martinicans and 94.9% of Guadeloupeans have detectable concentrations of CLD in their blood [7]. Several epidemiological studies were conducted to determine the health impact of this exposure. A correlation between pre- and postnatal chlordecone exposure and short-term memory and fine motor skills in young infants in the TIMOUN study [8–10]. CLD presents also endocrine disrupting properties [11] and is associated to type 2 diabetes [12]. Recent studies show that CLD exposure may be associated with altered epigenetic marks [13] and autoimmune diseases [14].

When CLD was prohibited in 1993, a weevil trap containing a pheromone, sordidin (**Figure 1**) was used [15]. Sordidin is a male-produced aggregation pheromone of banana weevil, related to ketal pheromones from Scolytids [15]. The production of this pheromone was first evidenced by Budenberg *et al.* in 1993. It was then identified and isolated in 1995 by Ducrot *et al*. as a major pheromone. Sordidin was first synthesized using the regioselective Baeyer-Villiger reaction of 2,6-disubstituted cyclohexanon as a key step, giving a mixture containing 4 stereoisomers. Trap system using this hormone is employed in the FWI and the Canary Islands. This trap supposes an interesting alternative mimicking the natural hormone allowing to substitute the use of CLD. A study of two plantations of over 200 hectares each shows a reduction in corm damage of 62.86% after the implantation of this biomimetic strategy [16].

The environmental problems produced by the CLD have led to the search for powerful and eco-friendly biomimetic pesticides as sordidin. These biomimetic pesticides should be: biodegradable (avoiding pest persistence); pest-specific; non-toxic to mammals and plants; and relatively less expensive in order to obtain a sustainable crop production.

Biomimetic compounds, as biopesticides, are obtained by synthetic routes which tend to transpose enzymatic reactions within the framework of synthetic organic chemistry. The concept of biomimetic synthesis of natural products was introduced by Robinson, following his straightforward synthesis of tropinone reported in 1917 [17, 18]. Several years later, the different ideas and the philosophy covering the biomimetic or biogenetic type synthesis was proposed by Van Tamelen in his work in 1961 [19]. Biomimetic synthesis can also describe a sequence of reactions carried out to

support a biogenetic hypothesis which is generally accepted with succeeded reactions [20]. Poupon, Nay and coworkers have compiled the biomimetic syntheses of several families of organic compounds including alkaloids [21], terpenoids, polyphenols and polyketides (as sordidin) [21]. Over past decades, numerous publications contain the biomimetic term associated with organic synthesis but also sensoring particularly in the pollution control field. For example, we may notice an increasingly use of molecular imprinted polymers as recognition elements in mimicking molecular/ionic recognition by natural receptors [22, 23]. Khadem *et al.* have designed an electrochemical selective sensor to determine the dicloran by modifying the working electrode with molecular imprinted polymer [24]. Liu *et al.* have developed a biomimetic absorbent containing the lipid triolein embedded in the cellulose acetate spheres to remove persistent organic pollutants from water [25]. More recently, Sicard *et al.* have proposed a strategy for the decontamination of organic pollutants combining pesticides and drugs based on the use of nucleolipids, polymer-free bioinspired materials. The advantage of using the latter lies in their degradation providing nontoxic natural biomolecules [21], such as nucleosides, phosphates, and lipids [26].

The present chapter shows a compilation of biomimetic and hemisynthetic pesticides, classified by several different mechanisms affecting one or more biological systems, including:

1. Pesticides targeting nervous system.

2. Pesticides targeting endocrine system.

3. Pesticides targeting digestive system.

4. Pesticides targeting different cellular structures.

2. Pesticides targeting nervous system

Insects have a simple nervous system with a brain linked to a ventral nerve cord that consists of paired segmental ganglia running along the ventral midline of the thorax and abdomen (**Figure 2**). An insect's brain is a complex of six fused ganglia located dorsally within the head capsule. These ganglia can be separated in 3 pairs:

- Protocerebrum, associated with vision.

- Deutocerebrum, processing sensory information collected by the antennae.

- Tritocerebrum, which innervate the labrum and integrate sensory inputs from proto-and deutocerebrums while also linking the brain with the rest of the ventral nerve cord.

Below the brain another complex of fused ganglia, the subesophageal ganglion innervates mandibles, maxillae, labium, the hypopharynx, salivary glands, and neck muscles. In the thorax, three pairs of thoracic ganglia control locomotion by innervating the legs and wings. Thoracic muscles and sensory receptors are also associated with these ganglia. Similarly, abdominal ganglia control movements of abdominal muscles [28]. In some insects, the thoracic ganglia fuse to form a single ganglion.

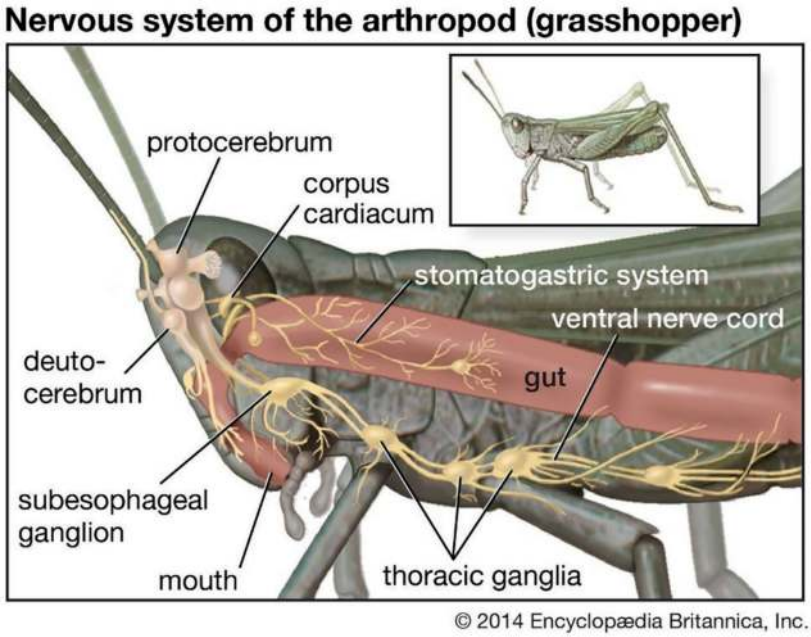


Figure 2.
Nervous system of the grasshopper [27].

Similarly, sometimes most of the abdominal ganglia are fused to form a single compound ganglion as in the blood sucking bug.

From molecular point of view, several receptors can be explored targeting the nervous system at different levels. These receptors are: i. Glutamate-gated chloride channels, ii. Voltage-gated sodium channels, iii. Transient receptor potential vanilloid channels, iv. Gamma-amino butyric acid receptors, v. Octopaminergic system and vi. Nicotinic acetylcholine receptors.

2.1 Glutamate-gated chloride channels (GluCls)

Glutamate-gated chloride channels (GluCls) are found only in protostome invertebrate phyla. Their functions include: the control and modulation of locomotion, the regulation of feeding, and the mediation of sensory inputs [29]. This channel is composed of 5 adjacent subunits. Each subunit is a polypeptide chain large extracellular N-terminal domain (for ligand binding) and four transmembrane domains (1–4) (**Figure 3**) [30].

2.1.1 Compounds acting via glutamate-gated chloride channels

- Avermectins and milbemycins:

Avermectins and milbemycins (**Figure 4**) are two families of hemisynthetic macrolides that have been widely used as pesticides in agriculture. The hemisynthesis of these molecules produces an increase of the chemical diversity starting from the natural ones produces by bacteria from the order Actinomycetes (as for example *Streptomyces avermitilis*). As an example of these molecules, we can mention aglycone milbemycin (**Figure 4**), abamectin, emamectin, doramectin,

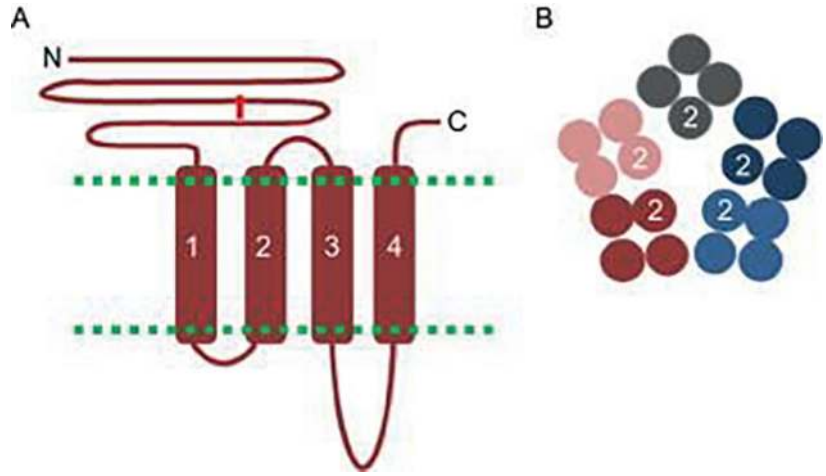


Figure 3.
Glutamate-gated chloride channels [31]. (A) Transmembrane scheme; (B) Scheme of top-view of channel.

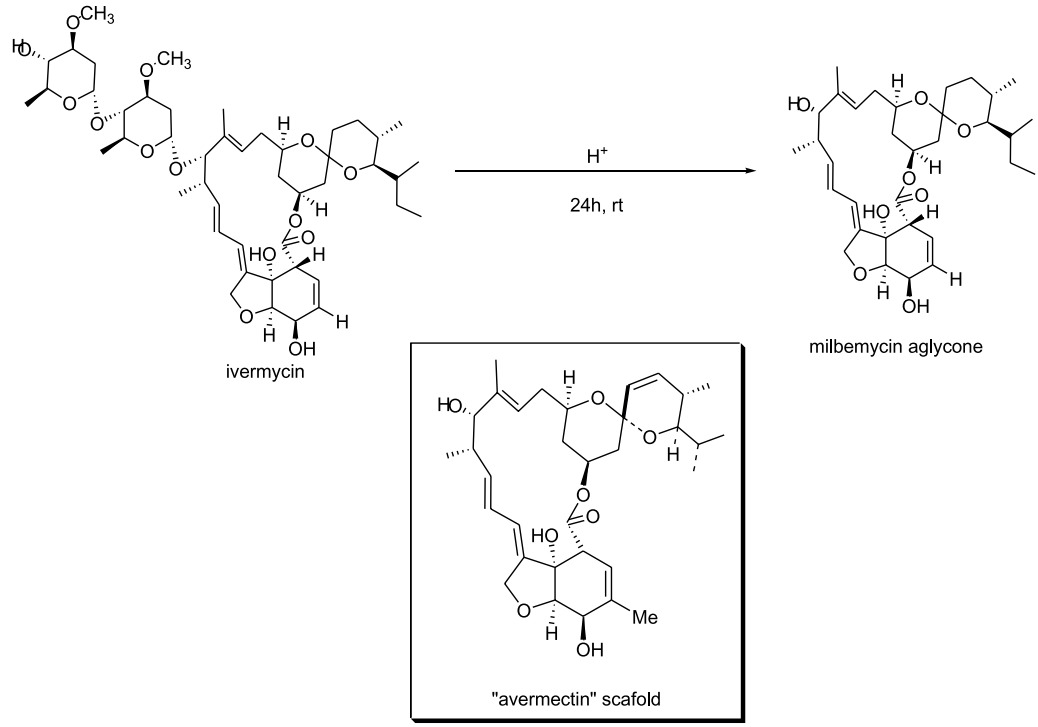


Figure 4.
Milbemycin aglycone synthesis [32].

milbemycin oxime, latidectin etc. These molecules attack the nervous system of insects [33]. This macrocyclic lactones exert their parasiticide (anthelmintic) and insecticidal effects mainly by potentiating the agonistic action of glutamate on GluCls or by directly activating GluCls, as in the case of *Drosophila melanogaster* [31], [34]. They act by linking to glutamate-dependent chloride channels common to invertebrate nerve and muscle cells. This binding causes the opening of the channels, increasing the flow of chloride ions and hyperpolarizing the cell

membranes, paralyzing and killing the invertebrate. **Figure 4** shows the hemisynthesis of aglycone milbemycin by solubilizing ivermectin in a concentrated sulfuric acid solution [32]. However, the milbemycins have characteristics that are harmless to the environment.

2.2 Voltage-gated sodium channels (VGSC)

The voltage-gated sodium channel (VGSC) mediates the increase in sodium conductance during the rapid depolarization phase of the membrane action potential (high concentration of sodium ions (Na^+) and a low concentration of potassium ions (K^+)). Therefore, this channel represents a key structural element that controls cellular excitability in biological systems [35]. Mammalian sodium channels are composed of a pore-forming α-subunit and one or more β-subunits. Sodium channel α-subunits have four homologous repeat domains (I–IV), each possessing six α-helical transmembrane segments (**Figure 5**). There are no orthologs of mammalian β-subunits in insects. Instead, the non-orthologous proteins TipE and three to four TipE-homologs (TEH1–4) seem to serve as auxiliary subunits of sodium channels *in vivo*. Structurally, both TipE and TEH1 have intracellular N- and C-termini and two transmembrane segments connected by a large extracellular loop [37]. In physiological function, the flow of sodium ions into and out of the insect synapse occurs through the sodium channel present on the cell membrane of the neuron. This flow is controlled by the normal movements of the insect's muscles. When the sodium channel is open, the muscle is activated, when it is closed, the muscle can relax.

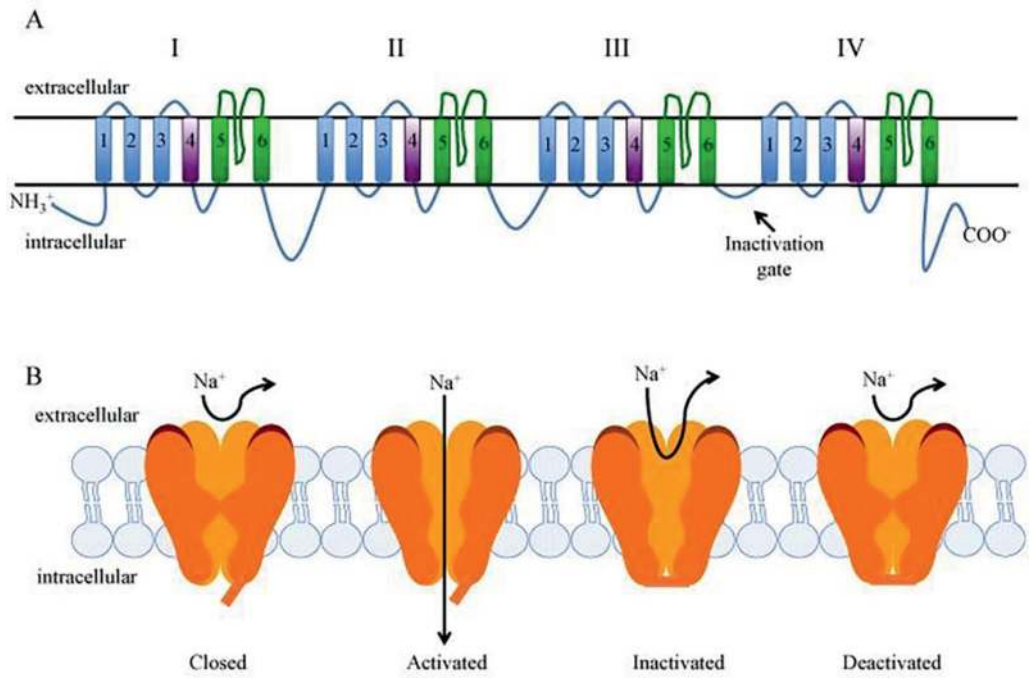


Figure 5.
The α subunit of the voltage-gated sodium channel. A. Structure of the subunit (four domains (I-IV) and their six transmembrane segments (1–6)). B. Four states of the VGSC (channel closed: at resting membrane potentials; activated or opened channel: During the rising phase of an action potential; inactivated channel: Falling phase; deactivated channel: During the undershoot phase prior to returning to the closed phase) [36].

2.2.1 Compounds acting via Voltage-Gated Sodium Channels

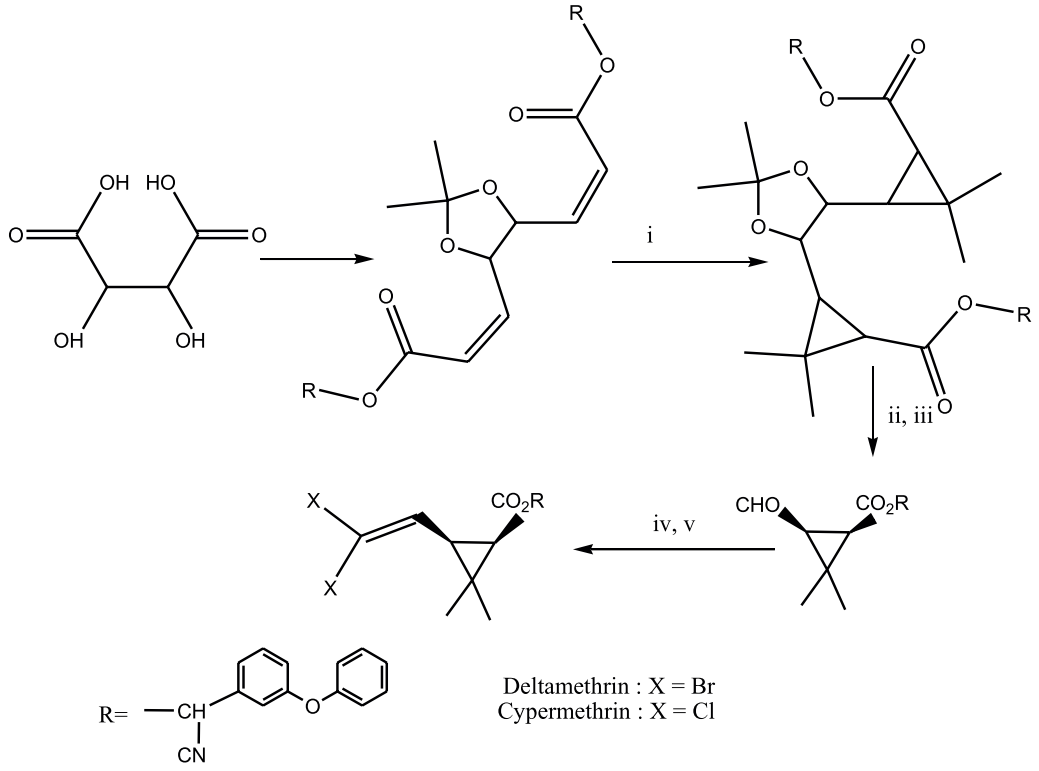
- Pyrethroids

Pyrethroids are biomimetic molecules adapted from natural pyrethrins isolated from the flowers of *Chrysanthemum cinerariifolium* [38]. Cypermethrin and deltamethrin are two examples of pyrethroid compounds. Their synthetical pathway consists of a cyclopropanation reaction of an α,β-unsaturated ester derived from D-glyceraldehyde, giving a hemicaronaldehyde, which subsequently leads to deltamethrin (**Figure 6**) [39].

Pyrethroids have been used in pest control as the main insecticides. The mode of action of pyrethroids consists in the binding and modulation of the activity of the VGSC, leading to a prolonged opening of sodium channels, and a continuous firing of action potential [40]. This neurotoxic action produces in the insect hyperactivity and convulsions, followed by lethargy, paralysis and death [41, 42].

2.3 Transient receptor potential vanilloid (TRPV) channels

The transient receptor potential vanilloid (TPRV) channel is a subfamily of 6 cationic channels. They are tetrameric and each subunit is composed of 6 transmembrane domains with 3 to 5 N-terminal ankyrin repeats and a TRP box in



(i) 2,5 equiv. $Ph_2S{=}C(Me)_2$; DME .-78°C; (ii) 4 equiv. 2Naq, $HClO_4$, THF,20°C,6h
(iii) 1,5 equiv, $NaIO_4$, MeOH, Phosphate buffer PH=7,2, 20°C, 1h. (iv) KOH, MeOH then aq,HCl
(v) CBr_4, PPH_3

Figure 6.
Deltametrin synthesis.

their C-terminal (**Figure 7**). The activation of TRPV1 primarily permits an influx of extracellular Ca^{2+}, which is involved in a number of essential physiological functions, such as neurotransmitter release, membrane excitability, and muscle cell contraction [44].

2.3.1 Compounds acting via TRPV Channels

- Afidopyropens

Afidopyropens (for example the keto-pyripyropene A) are new hemisynthetic insecticides derived from pyripyropene A (**Figure 8**). This family of molecules presents a strong insecticidal activity against aphids. These molecules modulate TRPV channels in the chordotonal organs of insects [46]. It is a class of ester molecules that are marketed under the common name of afidopyropen [47] including keto-pyripyropene A. The biomimetic hemisynthesis of keto-pyripyropene A is done as

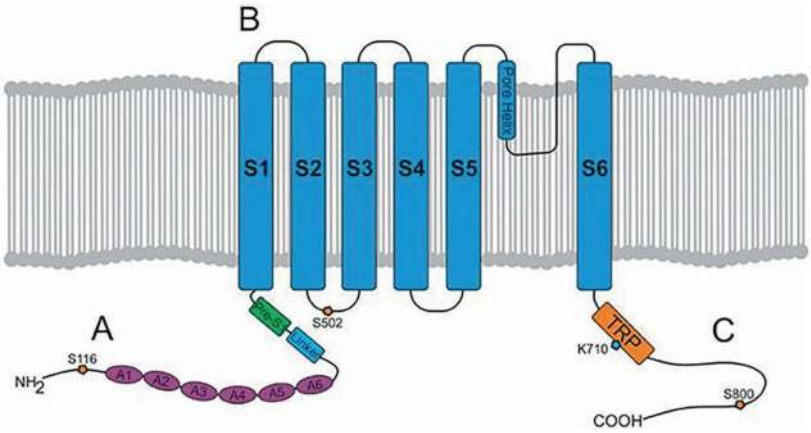


Figure 7.
Structure of a TRPV1 subunit. A. N-terminus containing 6 ankyrin subunits (A1–A6) and a linking region consisting of a linker and a pre-S1 helix segment. B. Transmembrane region with 6 helical segments (S1–S6). C. C-terminus containing a TRP domain and binding sites for protein kinase A, C, phosphatidylinositol-4,5-bisphosphate (PIP_2), and calmodulin [43].

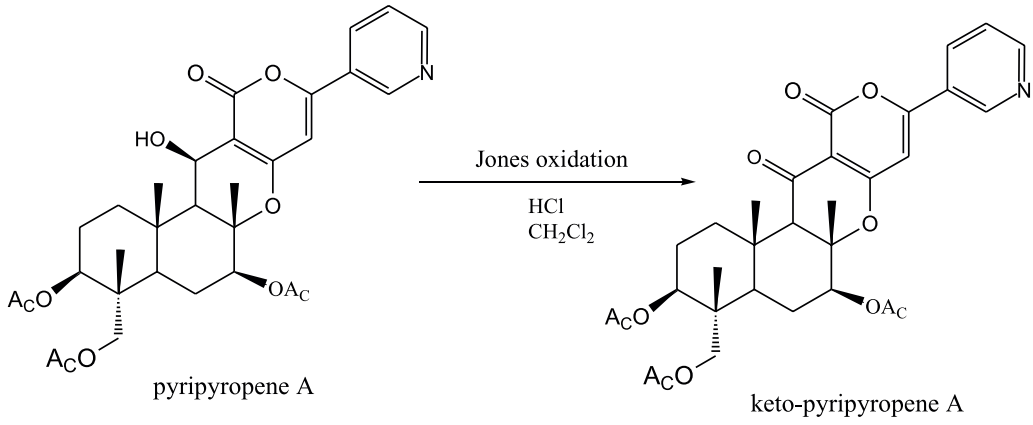


Figure 8.
Keto-pyripyropene A synthesis [45].

follows, a modification of pyripyropene A through a Jones oxidation allows to obtain keto-pyripyropene A (**Figure 8**) [45].

2.4 Gamma-amino butyric acid (GABA) receptors

The GABA receptors are located in the nervous system of many insects. It is an oligomer of 5 subunits (**Figure 9**), each being polypeptide with a large domain in their N-terminal and 4 transmembrane domains [49]. The binding of GABA on its receptors leads to the inhibition of the nerve impulse. GABA acts by binding to its specific transmembrane receptors (GABA-gated chloride channels) present in the plasma membrane of neurons, opens the chloride (Cl^-) channels to allow the flow of Cl^- into the neurons. This results in a negative charge on the transmembrane potential causing hyperpolarization and a reduction in membrane entry resistance. Pesticides by binding to insect GABA receptors, decrease or increase Cl^- influx into neurons, and kill insects by causing excessive excitation or inhibition of the nervous system (hyperactivity, hyperexcitability, convulsions, production of prolonged high frequency discharges, etc.) [50, 51].

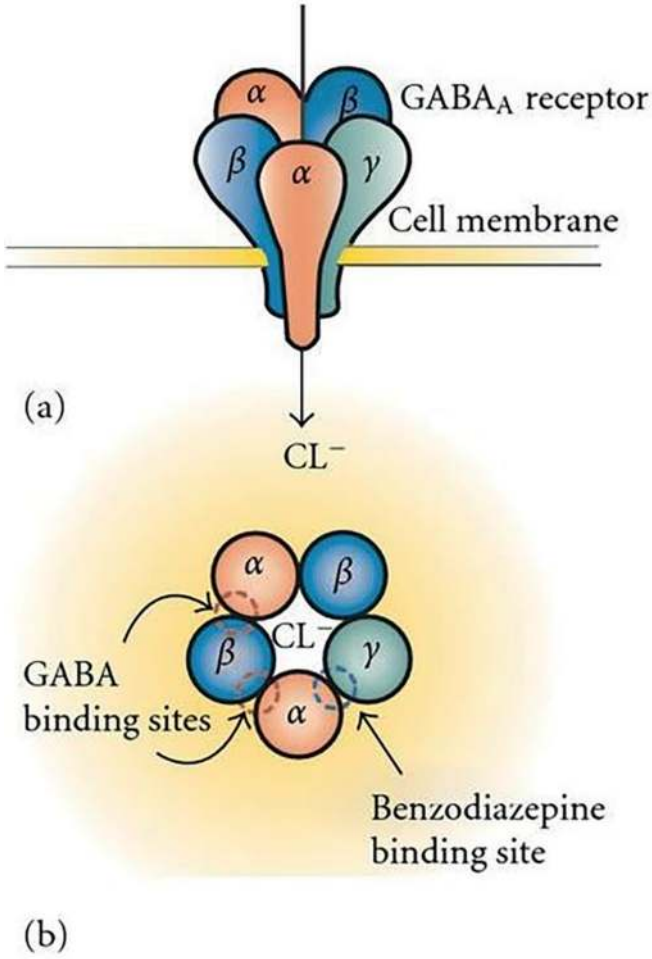
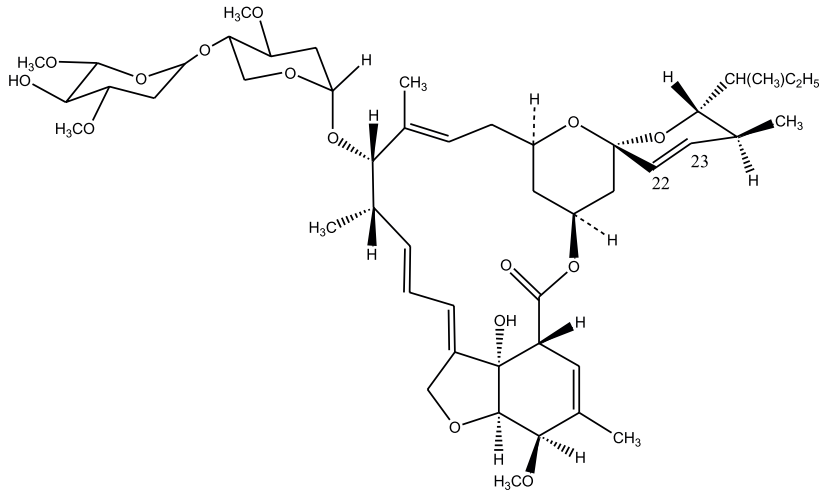


Figure 9.
Representation of the GABAA receptor structure. (a). The inhibitory GABAA receptor consists of five subunits that together form a ligand-gated chloride (Cl^-) channel. (b). The most common subtype is a pentamer with 2α,2β, and 1 γ-subunit [48].

2.4.1 Compounds acting via GABA receptors

- Avermectins

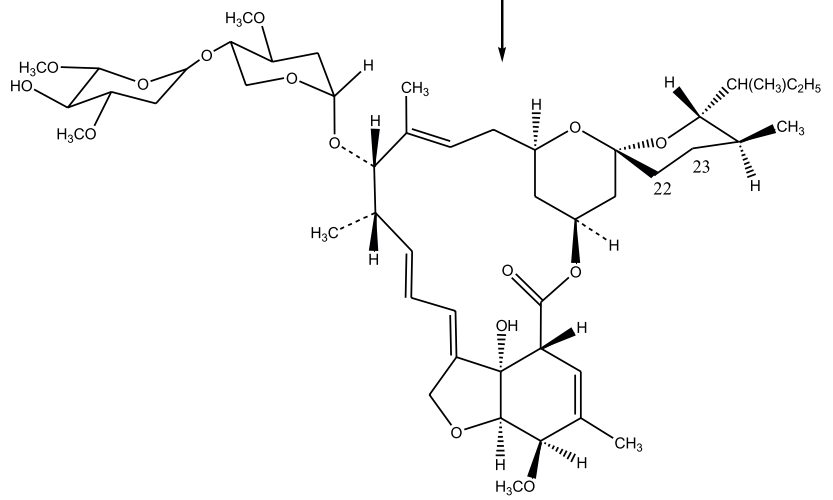
The avermectins are hemisynthetic pesticides acting on glutamate-gated chloride channels (GluCls) and gamma-amino butyric acid (GABA) receptors, and then causes neuromuscular paralysis that eventually leads to death [52]. Several derivates can be synthetized starting from avermectins. For example, the hydrogenation of avermectin



avermectin A_1

$(PH_3P)_3RhCl$
toluene

25°C



22,23-dihydroavermectin A_1

Figure 10.
Dihydroavermectin A_1 synthesis.

A_1 with Wilkinson's catalyst ($(PH_3P)_3RhCl$) [53] yields to the dihydroavermectin A_1 (**Figure 10**).

- Emamectin

Emamectin (**Figure 11**) is another hemisynthetic pesticide targeting the same receptors (GABA and GluCls) that the avermectins. The emamectin causes neuromuscular paralysis that eventually leads to death [23]. Emamectin activates chloride channels by stimulating high-affinity GABA receptors and GluCls channels, which increases membrane permeability to Cl^- and disrupts nerve signals in arthropods. This results in hyperpolarization and removal of signal transduction in the insect nervous system, which reduces neurotransmission [54]. The insect larva stops feeding after exposure and becomes irreversibly paralyzed which leads to death within 3 or 4 days [55].

2.5 Octopaminergic (OA) system

Octopamine is a neurohormone (released in the hemolymph for lipid mobilizing during flight and long-lasting motor behaviors), a neuromodulator and a neurotransmitter present in relatively high concentrations in every invertebrate tissue [56]. Octopamine binds to a specific G protein-coupled membrane receptor. The binding of octopamine to these receptors leads to the activation of the enzyme adenylyl cyclase. It transforms ATP to cAMP and causes an increase in the cAMP level, which is a signaling molecule, activating the protein kinase A (PKA). The G protein also activates phospholipase C (**Figure 12**). It leads to the release of calcium from deposits in the endoplasmic reticulum and to the elevation of its intracellular level as well as to the activation of the calcium-dependent protein kinase C (PKC). Protein kinases phosphorylate several enzymes and receptors leading to the modulation of their activity. This phosphorylation produces important changes in cell functions [57].

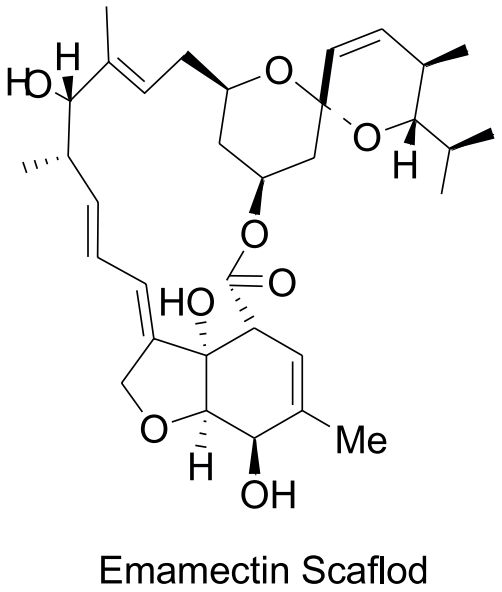


Figure 11.
Structure of emamectin.

2.5.1 Compounds acting via the Octopaminergic (OA) System

- Phenylpropanoids

Hemisynthetic phenylpropanoids derivatives can interfere with the octopaminergic system. Their binding to the octopamine receptor causes its blockage which leads to decreased cAMP levels within cells, thus resulting in antifeedant and larvicidal effect [58]. For example, the dillapiole, a phenylpropanoid isolated from the essential oil of leaves of *Piper aduncum* L. and several hemisynthetic derivatives present an activity against *Aedes aegypti* L. being several derivates more actives than the dillapiole [59]. Following a similar approach, Sinha's team designed a hemisynthetic method to obtain cinnamic esters from the oxidation of cinnamaldehydes (**Figure 13**).

Eugenol is a phenylpropanoid and a major constituent of clove oil (*Syzygium aromaticum* L.) with many applications in the pharmaceutical, food, agricultural and cosmetic industries [60]. Eugenol can mimic octopamine by increasing intracellular calcium levels in cloned brain cells of *Periplaneta americana* L. and *Drosophila melanogaster* Meigen [61].

2.6 Nicotinic acetylcholine receptors (nAChRs)

Nicotinic acetylcholine receptors (nAChRs) are ion channels that mediate fast neurotransmission in the central and peripheral nervous systems. nAChRs are

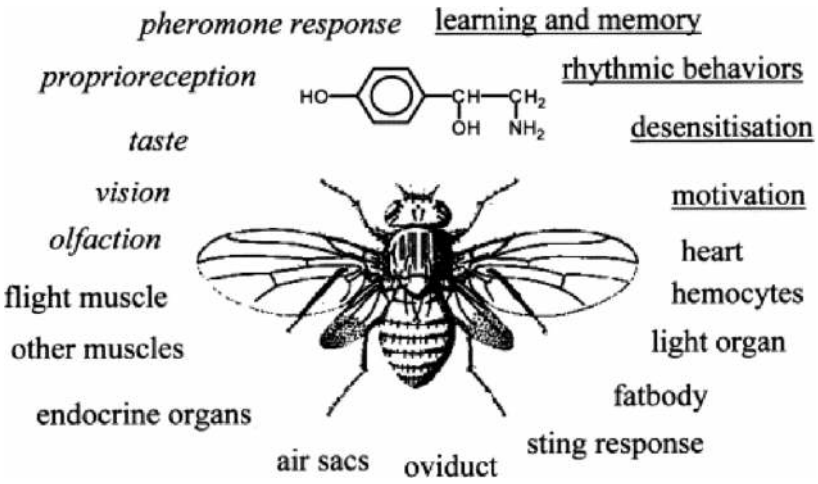


Figure 12.
Effects of OA on different tissues of invertebrates. Sense organs (italic); central systems (underlined) modulated by OA [56].

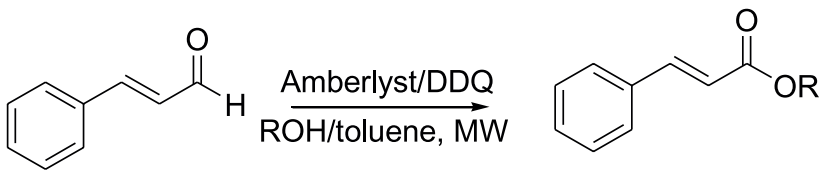


Figure 13.
Hemisynthesis of phenylpropanoids derivatives.

formed by the assembly of 5 transmembrane subunits (**Figure 9**) among 17 different nAChR subunits. nAChRs regulate the flow of mainly sodium, potassium and calcium ions across the cell membrane (**Figure 14**) [62].

2.6.1 Compounds acting via nicotinic acetylcholine receptors

- Flupyradifurone

Flupyradifurones are a class of synthetic butenolide insecticides, mimic of natural neonicotinoids, active against various pests and suckers with an excellent safety profile. It acts reversibly as an agonist on the nicotinic acetylcholine receptors of insects. It binds to the nAChR blocking it. Flupyradifurone is a

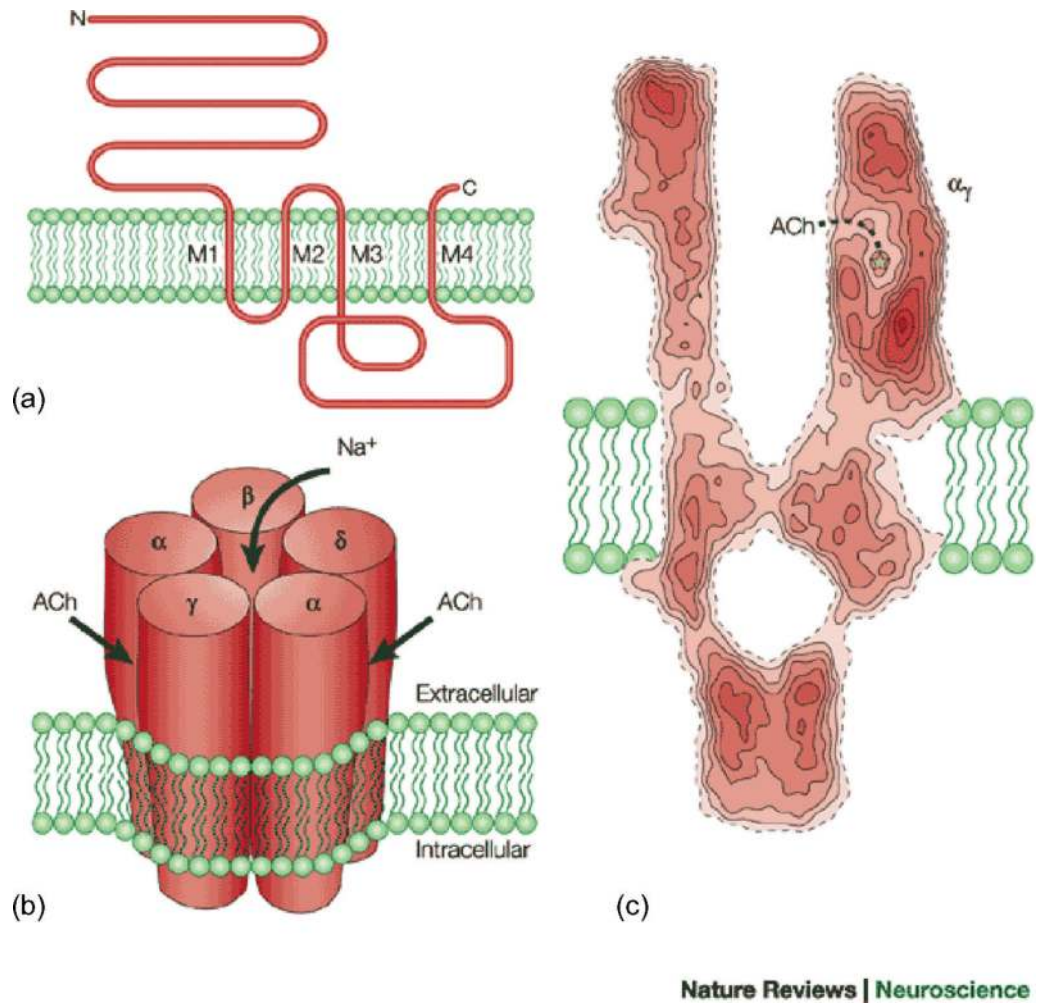


Figure 14.
Structure of the nicotinic acetylcholine receptors. (a). The threading pattern of receptor subunits through the membrane. (b). A schematic representation of the quaternary structure, showing the arrangement of the subunits in the muscle-type receptor, the location of the two acetylcholine (ACh)-binding sites (between an α- and a γ-subunit, and an α- and a δ-subunit), and the axial cation-conducting channel. (c). A cross-section through the 4.6-Å structure of the receptor [63].

novel butenolide insecticide that is also systemic and a nicotinic acetylcholine receptor (nAChR) agonist. Tosi and Nieh [64] provide the first demonstration of adverse synergistic effects on honeybee survival and behavior (*Apis mellifera* L.) (poor coordination, hyperactivity, apathy). Two different pathways for the synthesis of flupyradifurone are presented in **Figure 15**. Starting from tetronic acid, one approach consists in two consecutive reactions. Where the tetronic acid reacts firstly with a difluoroethane-1-amine and secondly with 2-Chloro-5-(chloromethyl)pyridine (Method A, **Figure 15**). And the other approach, where the tetronic acid reacts with difluoroethane-1-amine derivative in the presence of 4-toluenesulfonic acid in a "one pot" approach (Method B, **Figure 15**) to yield flupyradifurone [65].

- Triflumezopyrim

Triflumezopyrim is biomimetic mesoionic insecticide, containing domains characteristics of natural betaines that have shown excellent control of sucking insects. Mesoionic insecticides bind to the orthosteric site of the nACHR and act primarily by inhibition of the binding site. A method for the synthesis of these pyrimidones is described as follows: 2-aminopyridine reacted with pyrimidine-5-carbadehyde to form imine, the imine was exposed to reductive amination conditions to generate amine which reacts with malonic chloride to form triflumezopyrim (**Figure 16**) [66].

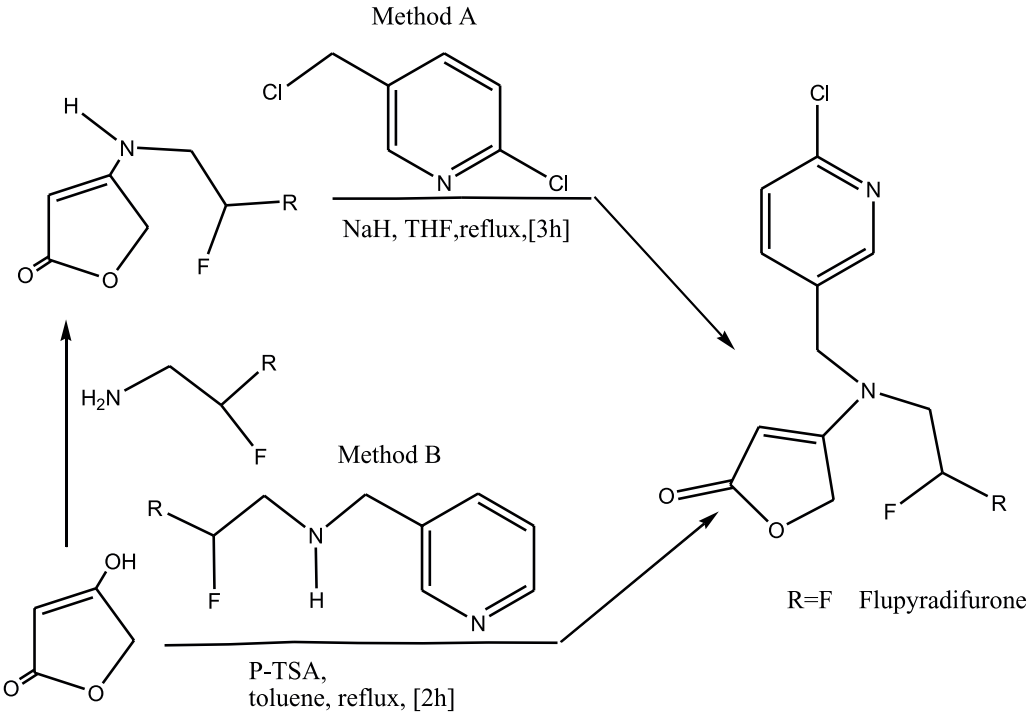
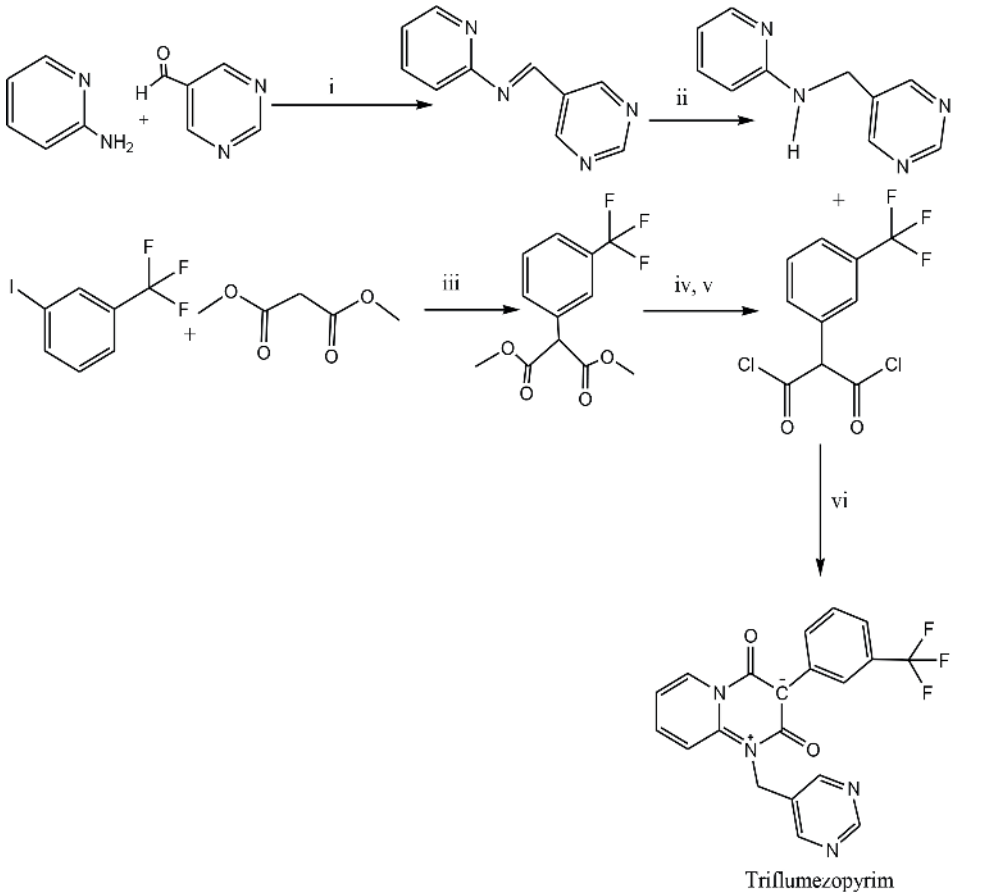


Figure 15.
Flupyradifurone synthesis.



Reagents and conditions: i) $CHCl_3$, 25°C ,99%; ii) $NaBH_4$, MeOH, THF,rt, 64% ; iii) CS_2CO_3, CuI (cat), 1,4-dioxane,90°C, 58%; iv) aq, KOH, 2-25°C, drying, 97%, v) $(COCl)_2$, DMF, (cat), toluene, 3°C to rt; vi) TEA, toluene, 3-25°C, 50% for 2 steps starting from the malonate salt

Figure 16.
Triflumezopyrim synthesis.

3. Pesticides targeting endocrine system

Complementary to the nervous system, the endocrine system ensures the functioning of the organism thanks to the production and the transport of various hormones trough the body. There are types of endocrine glands: neurosecretory cells within the central nervous system whose secretions act on effector organs or on other endocrine glands and specialized endocrine glands, *corpora cardiaca*, *corpora allata*, and the prothoracic glands [67].

3.1 Apoptosis

Apoptosis is a programmed cellular death occurring under regulated conditions. At the end of the process, the cell divides in many apoptotic bodies that will be phagocyted. Caspases (cysteine aspartate-specific proteinases) are a family of cysteine proteases that serve as both the initiators and the executioners of apoptosis. They are crucial mediators of apoptosis, and their activation is carefully controlled

by a death program. An unbalance in this program can lead to deleterious apoptosis [68]. Caspases are frequently considered synonymous with apoptotic cell death [69], but the review of Accorsi, 2015 [70] prove that these proteases may exert their activities in non-apoptotic functions (developmentally regulated autophagy during insect metamorphosis, neuroblast self-renewal and the immune response).

3.1.1 Compounds acting via apoptosis

- Phenylpropanoids

Several amino-alcohols biomimetic derivates of the phenylpropanoid eugenol are insecticides that act against *Spodoptera frugiperda* Smith and increase the activity of caspases leading to apoptosis [71]. The amino-alcohols are derivatives obtained by a hemisynthetic reaction of eugenol. In this reaction eugenol was converted to the corresponding epoxide with *m*-chloroperoxybenzoic acid (*m*-CPBA) in dichloromethane and then reacted with a series of nucleophilic amines to give the corresponding β-amino alcohols (**Figure 17**) [71].

3.2 Ecdysteroids

Steroid hormones play indispensable roles in modulating a broad range of biological processes in nearly all multicellular organisms. Once produced, steroid hormones are circulated in hemolymph and are easily transported to target cells to act as ligands for the nuclear receptor family of transcription factors. In insects, the major steroid hormones are ecdysteroids, also known as molting hormones (**Figure 18**). They play essential roles in coordinating developmental transitions, such as larval molting and metamorphosis (**Figure 13**) [73].

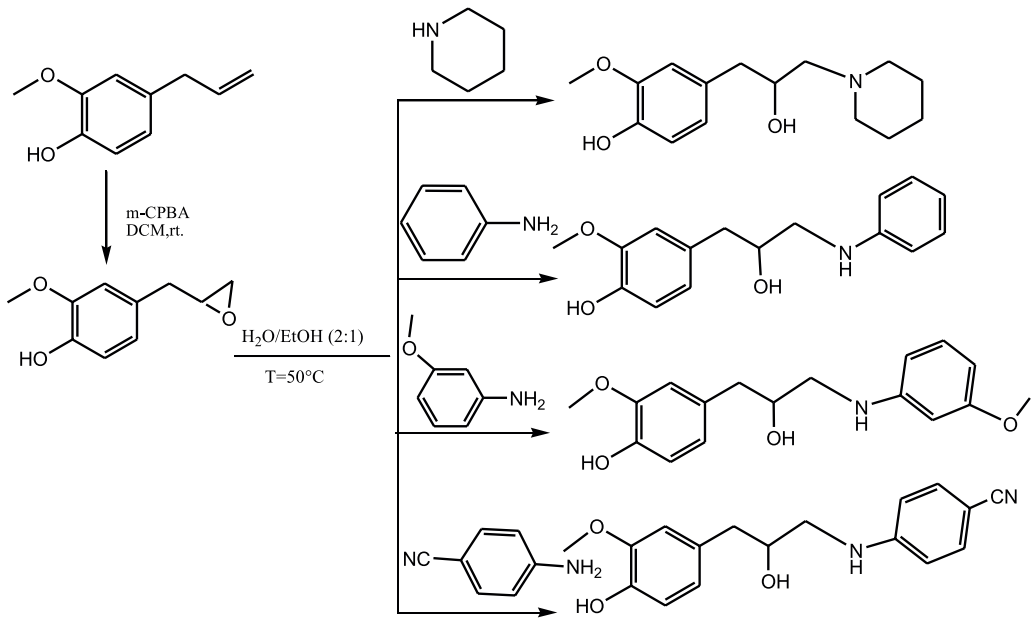


Figure 17.
Hemisynthesis of eugenol alcohols.

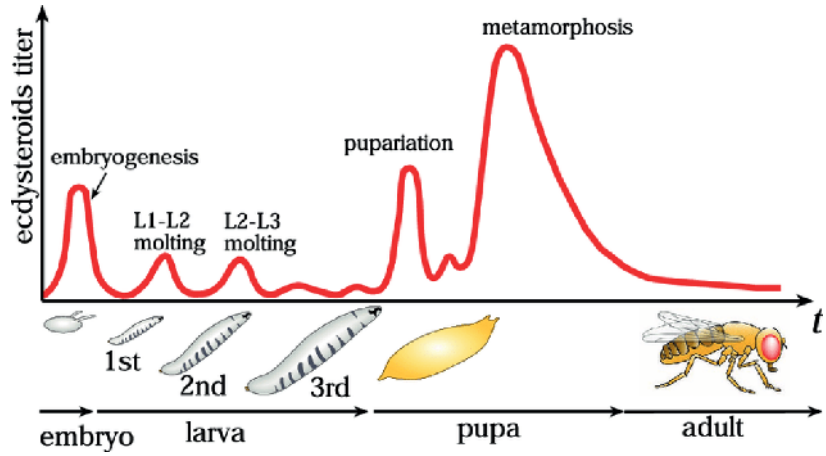


Figure 18.
The developmental stages and ecdysteroid titers in D. melanogaster [72].

The different metamorphoses undergone by insects to pass from one stage to another (larval stage to metamorphosis) are called molts (ecdysis). Molting takes place under the control of steroid hormone (ecdysone) responsible for molting [74] and the juvenile hormone (JH), responsible for inhibiting the steroid hormone to maintain the insect in its larval state and thus avoid premature ecdysis [75]. Activation and release of ecdysone into the hemolymph are controlled by the prothoracic hormone (PPTH), produced by the *corpora cardiaca*, and the insect insulin.

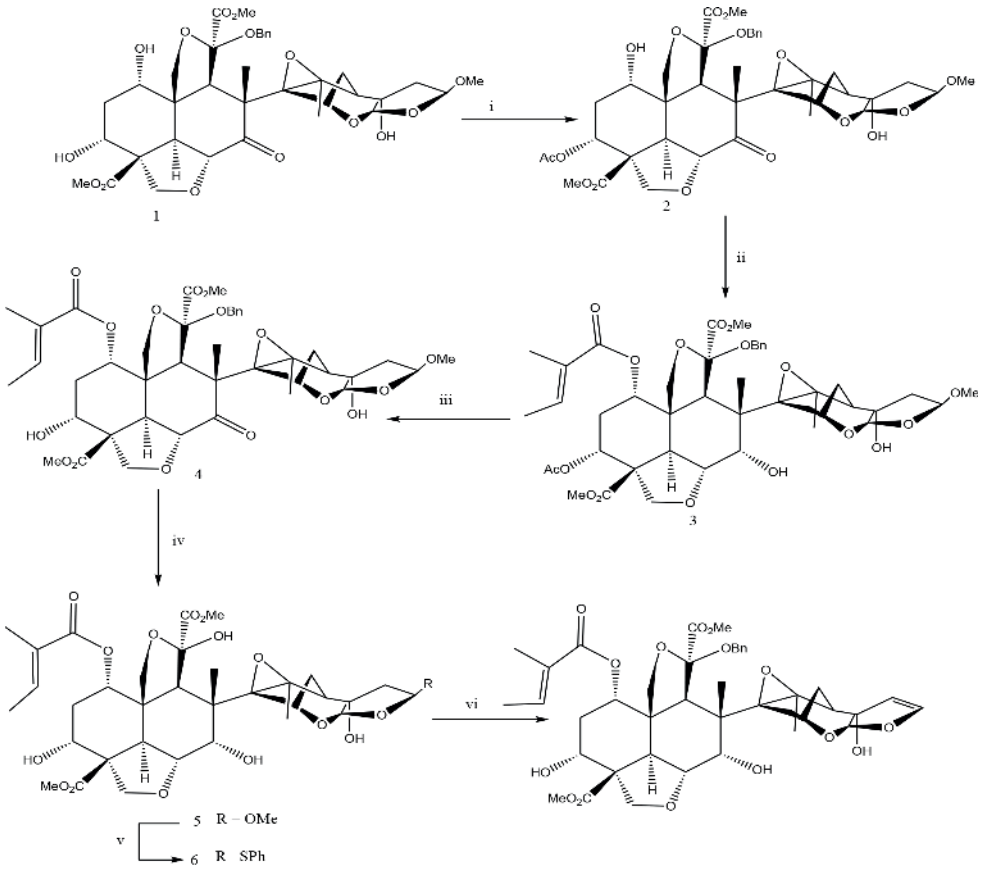
3.2.1 Compounds acting via ecdysteroids

- Azadirachtin-A derivatives

Tetrahydroazadirachtin, alongside with other azadirachtin-A analogues like 22,23-dihydroazadirachtin; 3-tigloylazadirachtol; 11-methoxydihydroazadirachtin and 22,23-bromoethoxydihydroazadirachtin are hemisynthetic pesticides disrupting the endocrine system. By blocking the release of neurosecretory peptides which regulate synthesis of ecdysteroids and juvenile hormone they provoke molt disruption leading to death [76].

Azadirachtin causes a slowdown in the synthesis and release of prothoracicotropic hormone (PPTH), which affects the functioning of the nucleus of secretory neurons and endocrine glands and the insect can no longer molt. Azadirachtin also modifies the production and stop of the growth functions [77].

Azadirachtin is a synthetic insecticide that belongs to the triterpenoid class of limonoids. One method of synthesis of azadirachtin starts with the selective acetylation in C3 of the triol to give the acetate derivate which by a series of reactions gives the triglate intermediate. Cleavage of the benzyl ether from the triglate intermediate occurred to provide lactol. Then the conversion of methyl acetal into phenyl sulfide during a treatment with thiophenol and catalytic PPTS (pyridinium toluene-P-sulfonic acid) in toluene followed by an oxidation with dimethyldioxirane (DMDO) followed by a pyrolysis to obtain azadirachtin (**Figure 19**) [78].



Reagents and conditions : (i) Ac_2O. Et_3N, DMAP, CH_2Cl_2, r.t.; (ii) $CH_3CH(CH_3)(CO)O(CO)C_6H_2Cl_3$, CS_2CO_3, toluène, reflux, (iii)$NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0°C. (iv) Pd/C, H_2, MeOH, r.t.; (v) PhSH, PPTS, CH_2ClCH_2Cl, 80°C, (vi) DMSO, CH_2Cl_2, -78°C, toluène reflux.

Figure 19.
Azadirachtin synthesis.

4. Pesticides targeting cellular structure

4.1 Chitin metabolism

Chitin is one of the most important natural biopolymers. It is mainly produced by fungi, arthropods, and nematodes. In insects, it supports the cuticles of tissues like the epidermis or the trachea. As for bones in the vertebrates, chitin is constantly synthesized and degraded. This balance is strictly controlled by the production of chitin synthases and chitinolytic enzymes to ensure a correct growth [79]. Chitin is widely distributed in the fungal kingdom since nearly all fungi have significant amounts of chitin in their cell wall (**Figure 14**). Cell wall architecture is well documented and it was described several decades ago that inhibition of chitin synthesis produces cell death [80]. Regarding the importance of chitin in growth and development of insects and in fungi cell wall, its synthesis is an interesting target for a pesticide. Chitin plays a key role in the insect's water system. It controls water homeostasis. The loss of this impermeable layer leads to transpiration which is fatal for the insect (**Figure 20**) [81].

4.1.1 Compounds acting via chitin metabolism

- N-amino-maleimide

N-amino-maleimide derivatives containing a hydrazone group are imides mimicking the synthesis of linderone and methyllinderone which were isolated from *Lindera erythrocarpa* M. Makino. They are fungicides that inhibit chitin synthase B-1,3-glucan synthase, leading to an alteration of the cell walls of fungi. A hemisynthetic method is described as follows: various aryl-substituted unsaturated ketones were synthesized and reacted with N-amino-maleimide under reflux of dry ethanol with a catalytic amount of *p*-toluenesulfonic acid to produce a variety of N-amino-maleimide derivatives containing a hydrazone group (**Figure 21**) [83].

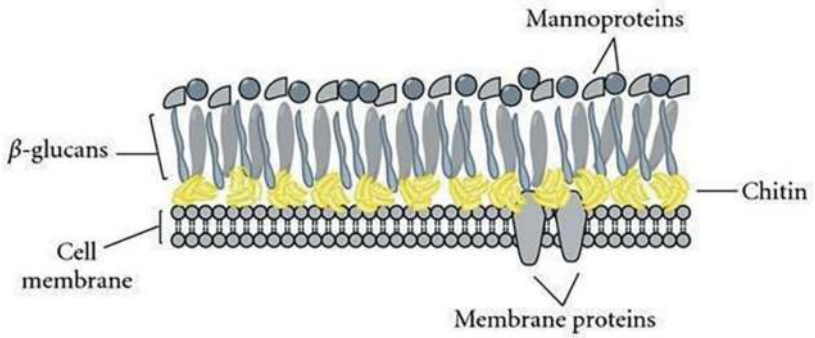


Figure 20.
Fungal cell wall components [82].

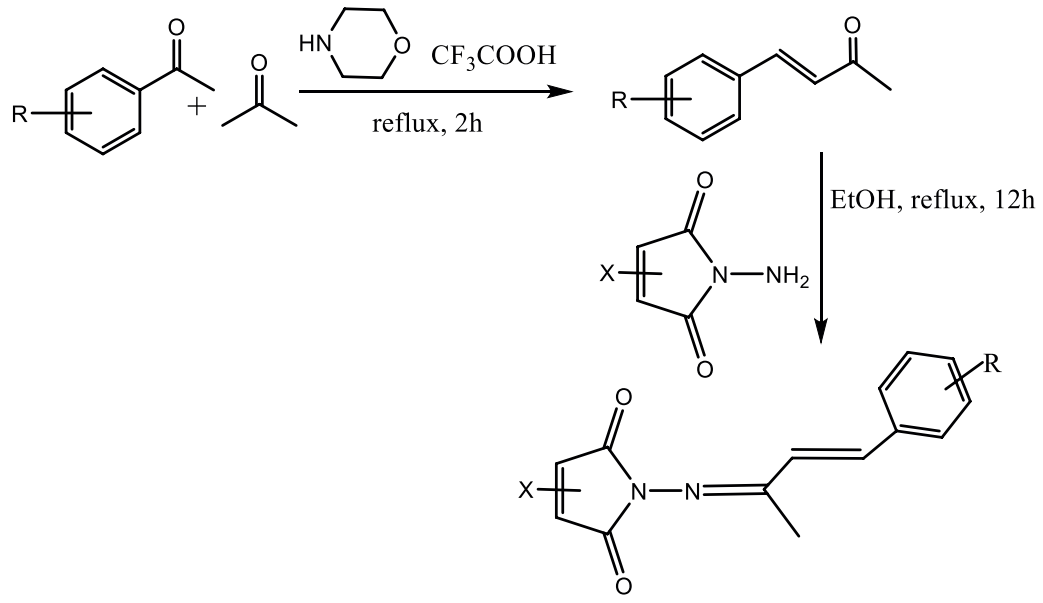


Figure 21.
Synthesis of N-amino-maleimide derivatives containing a hydrazone group.

4.2 Cell membrane

In any living being, the cell membrane ensures the smooth-running of the exchanges between the cytoplasm and the extracellular matrix. It is composed of a lipid bilayer containing proteins, glycoprotein, glycolipids and sterols. The latter are important component of the cell membrane, they regulate its fluidity and the enzymes in it (like the chitin synthases) [84].

4.2.1 Compounds acting via the cell membrane

- Spiroxamine

Spiroxamine is a synthetic fungicide mimic of the class of natural or synthetic morpholines such as fenpropidin, tridemorph, fenpropimorph etc. It inhibits both delta-14 reductase and delta-7–delta-8 isomerase, which leads to the formation of carbocation sterols, and strongly affects hyphae and mycelium development [85]. One method of synthesis of this molecule is as follows, tert-butyl cyclohexanone is first reacted with 3-chloro-1,2-propanediol. Formation of the ketal under acidic conditions leads to 8-tert butyl-1,4-dioxanspiro[4,5]decan-2-ylmethyl chloride, which is reacted with ethyl propylamine to form spiroxamine following nucleophilic substitution (**Figure 22**) [86].

- Prochloraz

Nitrogen compounds such as prochloraz (imidazole), fenarimol (pyrimidine), epoxyconazole, fluzilazole, and tebuconazole (triazole) are synthetic fungicides that act on essential fungal functions. They are inhibitors of the α-methylation of sterols [84]. Prochloraz for example is a fungicide of the imidazole family which can be obtained in several steps. Initially 2,4,6-trichlorophenol is alkylated with 1,2-dibromomethane in a Williamson ether synthesis. The following reaction with propylamine provides a secondary amine which is reacted with phosgene. This acid chloride of a carbamic acid is finally reacted with imidazole to give prochloraz (**Figure 23**) [87].

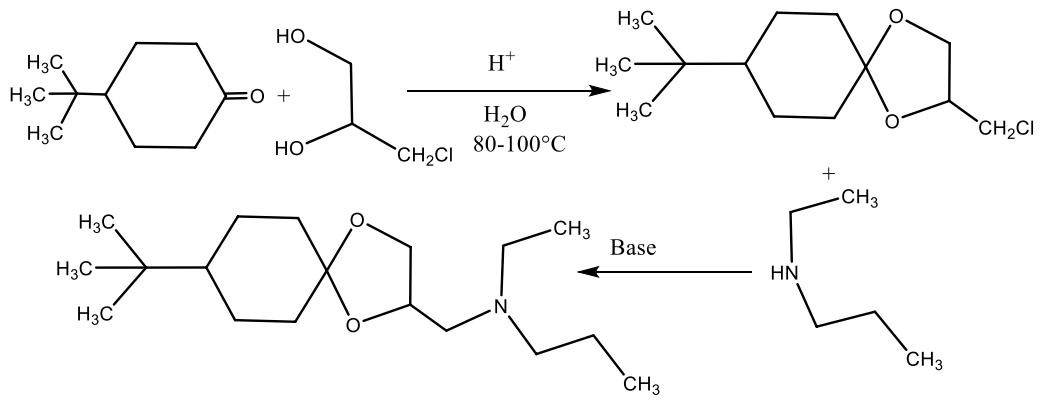


Figure 22.
Spiroxamine synthesis.

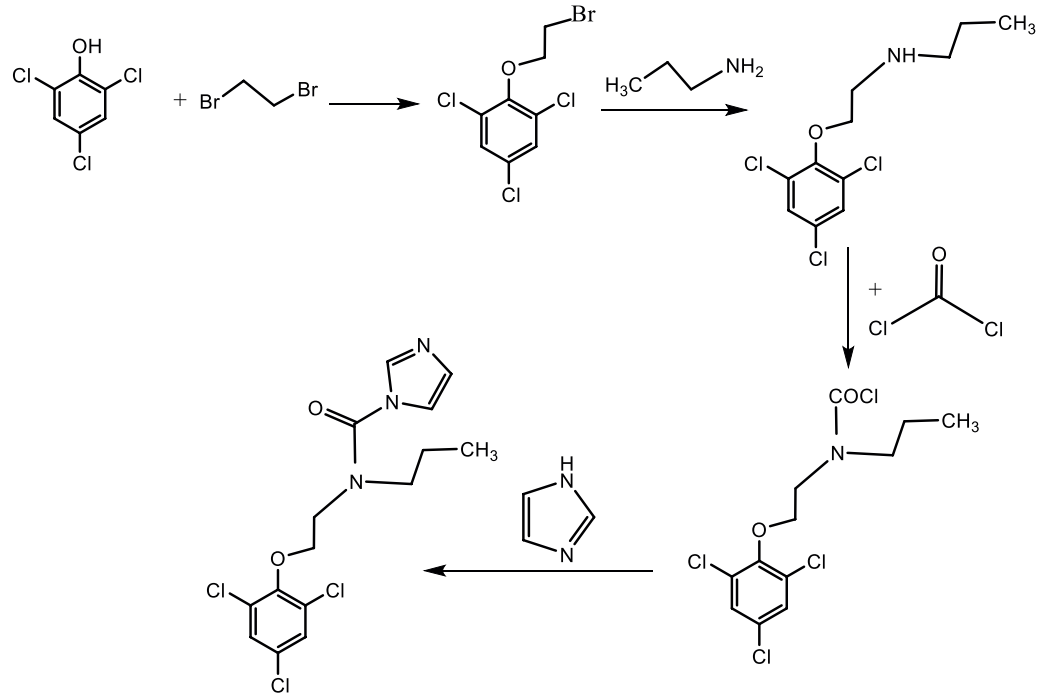


Figure 23.
Prochloraz synthesis.

4.3 Cytoskeleton

The cytoskeleton and membrane systems of eukaryotic cells play key roles in the intracellular transport of vesicles, organelles, and macromolecules. The actin cytoskeleton is mainly composed of globular actin (G-actin), which is monomeric actin able to self-assemble into filamentous actin (F-actin) [88]. The actin cytoskeleton is subjected to alterations and organizations to promote cellular dynamic and particle transport within and between cells. Eukaryotic cells polymerize actin filaments to provide mechanical integrity and motility force for a wide range of cellular mechanisms [89]. Microtubules are the main components of the cytoskeleton and the spindle apparatus (the cytoskeletal structure separating the sister chromatids during cell division). They are formed through α−/β-tubulin heterodimers assembling into cylindric filaments (**Figure 24**). The plus-ends of these filaments grow pointing towards the plasma membrane into protrusions, while their minus ends are anchored at microtubule-organizing centers (MTOCs) such as the centrosome. This polarity allows selective directional long-range cargo transport at the cell periphery [88]. Any substance able to impair with the formation or functioning of those microtubules blocks cell division in general and hyphae in fungi [84].

4.3.1 Compounds acting via the cytoskeleton

- Carbendazim

Carbendazim is a biomimetic benzimidazole that inhibits microtubule assembly and therefore blocks cell division in fungi. This effect appears to be related to their β-tubulin

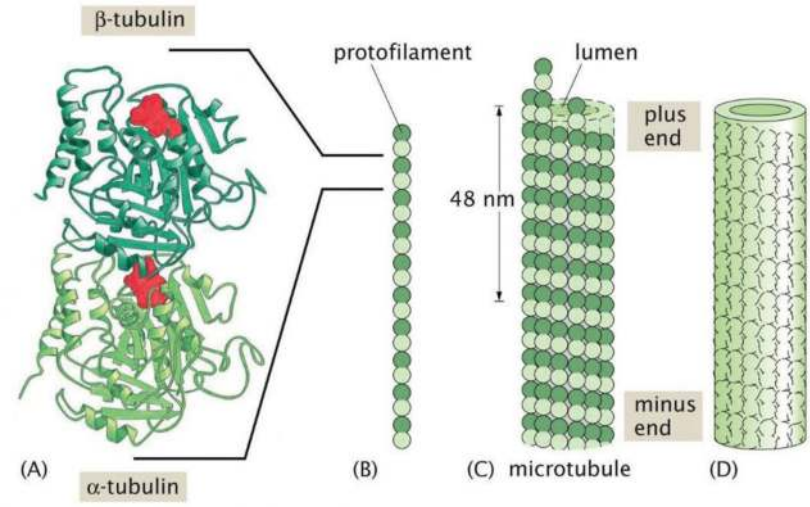


Figure 24.
Microtubules formation: A. Tubulin dimerization; B. Tubulin dimers polymerization; C. Protofilament association; D. Formed microtubule [90].

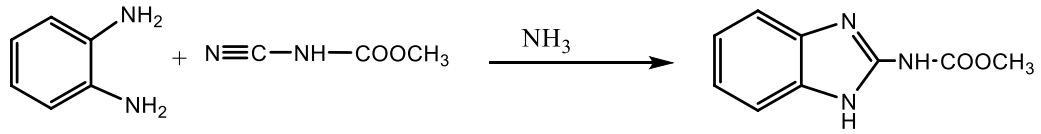


Figure 25.
Carbendazim synthesis.

binding, the main component of microtubulins. Carbendazim binds to β-tubulin and prevents tubulin formation [84]. A simple way to synthesize this molecule was realized by the condensation of orthophenylene diamine with an ester of aminonitrile in the presence of ammonia according to the figure below (**Figure 25**) [91].

Carbendazim is a widely used broad-spectrum fungicide that inhibits mitotic microtubule formation and cell division. The use of proteomics approaches, suggest that carbendazim is an environmental risk factor that likely weakens honeybees (*Apis mellifera*) colonies, partially due to reduced expression of major royal jelly proteins, which may be potential causes of colony collapse disorder [92].

- Ethylicin

Biomimetic organosulfur compounds have received considerable attention in recent years. Among various organosulfur compounds have shown a broad spectrum of biological activity such as fungicidal activity [93, 94]. They can block the normal metabolism of microorganisms by sulfenylation of the thiol groups of enzymes [95, 96]. Ethylicin is therefore a biomimetic organosulfur fungicide with a broad spectrum for plants. It can inhibit the growth of *Pseudomonas syringae* pv. *actinidiae* and prevent cancer in the plant stem [97, 98]. It is a bionic organosulfur pesticide (S-ethyl ethanethiosulfonate) that mimics the natural allicin obtained from garlic (*Allium sativum* L.). It was first prepared and studied in the laboratory during the synthetic research of allicin and its homologs in 1958 and developed as a broad spectrum biomimetic fungicide in China [99]. Because of the widespread application

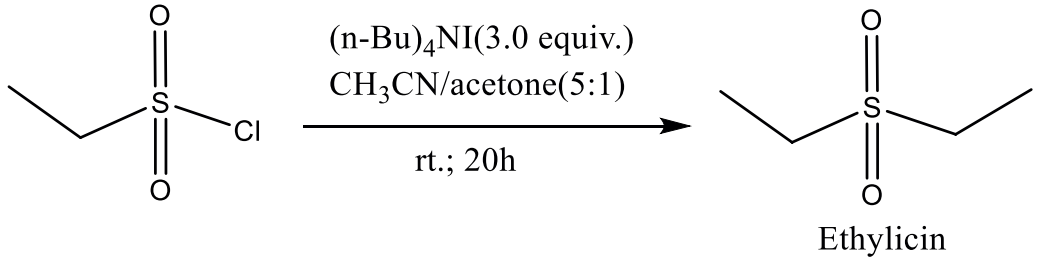


Figure 26.
Ethylicin synthesis.

of thiosulfonates, considerable effort has been made to develop synthetic methods for these compounds. Therefore, one of the synthesis methods used is the reduction of sulfonyl chlorides (**Figure 26**) [100].

5. Pesticides targeting digestive system

All insects have a complete digestive system in the form of a tube-like enclosure. Named the alimentary canal and running lengthwise through the body from mouth to anus, it consists of three regions: the foregut or stomodaeum, the midgut or mesenteron, and the hindgut or proctodaeum (**Figure 21**). An insect's mouth, located centrally at the base of the mouthparts, is a sphincter that marks the "front" of the foregut. Then goes the pharynx, from which food passes into the esophagus, a simple tube that connects the pharynx to the crop, a food-storage organ where food remains until it can be processed through the remaining sections of the alimentary canal. In some insects, the crop opens posteriorly into the proventriculus, which grinds and pulverizes food particles before they reach the stomodeal valve, a sphincter regulating the flow of food from the stomodeum to the mesenteron. The midgut begins just past the stomodeal valve. Near its anterior end, finger-like projections (usually from 2 to 10) diverge from the walls of the midgut. Gastric caecae provide extra surface area for secretion of enzymes or absorption of water (and other substances) from the alimentary canal. The rest of the midgut is called the ventriculus — it is the primary site for enzymatic digestion of food and absorption of nutrients. Digestive cells lining the walls of the ventriculus have microscopic projections (microvilli) that increase surface area for nutrient absorption. The posterior end of the midgut is marked by another sphincter muscle, the pyloric valve. It serves as a point of origin for dozens to hundreds of Malpighian tubules. These long, spaghetti-like structures extend throughout most of the abdominal cavity where they serve as excretory organs, removing nitrogenous wastes from the hemolymph (analog of blood in arthropods). The rest of the hindgut plays a major role in homeostasis by regulating the absorption of water and salts from waste products in the alimentary canal (**Figure 27**) [101].

5.1 Compounds acting *via* the digestive system

- Triterpenic derivatives

Balanced nutritional intake is essential to ensure that insects undergo adequate larval development and metamorphosis. Terpenes are a class of hydrocarbons,

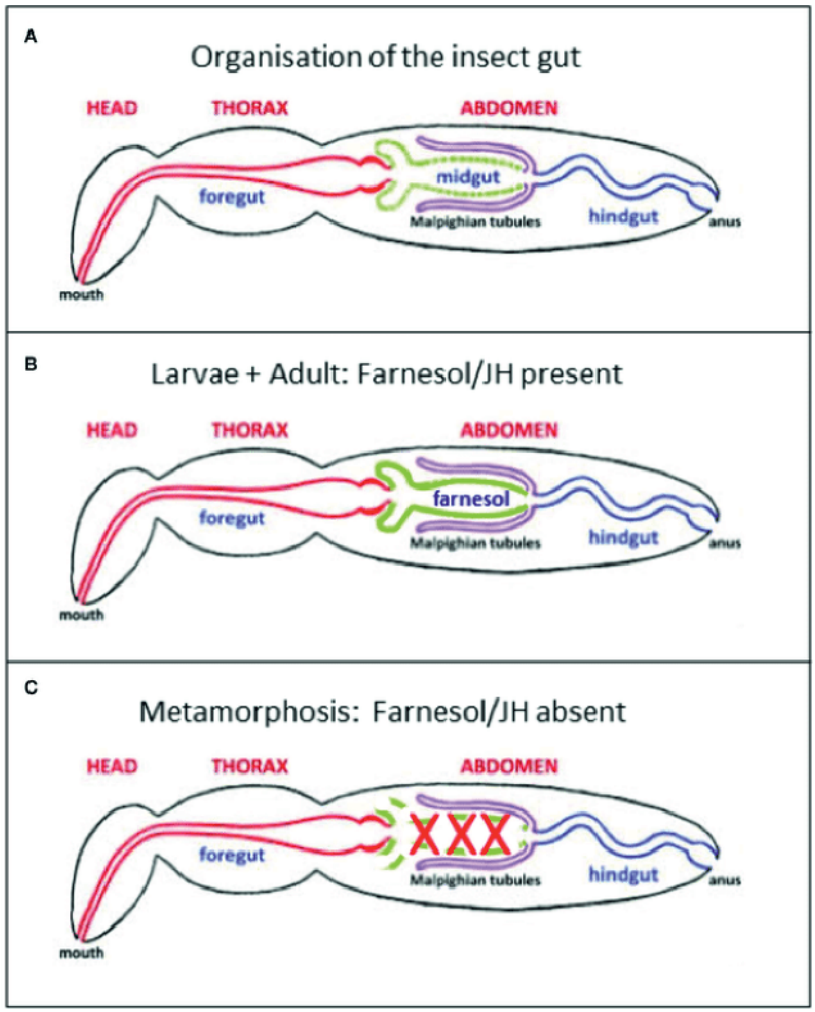


Figure 27.
Generalized insect digestive system illustrating the three main regions at different stages of development [102] (JH = juvenile hormone).

produced by many plants. The aim is to optimize insecticidal triterpene derivatives by biomimetic oxidation with hydrogen peroxide and iodosobenzenes catalyzed by porphyrin complexes. Therefore, the hemisynthesis of the derivatives were made from 31-norlanosterol an insecticide isolated from the latex of *Euphorbia officinarum* L. and were subjected to oxidation with hydrogen peroxide (H_2O_2) and iodosobenzene (PhIO) catalyzed by porphyrin complexes following a biomimetic strategy. Main transformations were epoxidation of double bonds and hydroxylations of non-activated C-H groups as shown in **Figure 12** [103]. These compounds caused a decreased digestive enzyme secretion and histolysis of intestinal tissues and led to indigestion, nutritional deficiency and decreased body weight of larvae. This prevented the larvae from reaching a critical weight and a normal population [103]. Similarly, work carried out on the development of *Chlosyne lacinia* caterpillars fed on *Heliantheae* leaves showed that the main discriminating metabolites of these leaves, diterpenes, caused a delay in the complete development of the caterpillars to the adult phase and that the latter showed a higher rate of diapause (**Figure 28**) [104].

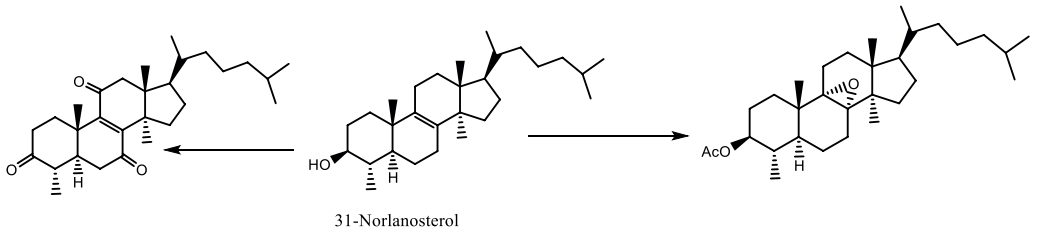


Figure 28.
Triterpenic derivatives synthesis.

6. Electron transport chain

Mitochondria regulate critical cellular processes, from energy production to apoptosis; within these organelles, sugars and long chain fatty acids are broken down, ADP is recycled back into ATP, steroids and lipids are synthesized, ancient DNA is replicated, transcribed and proteins are translated, along with numerous other reactions that are essential for human life [105]. Characteristic properties of all insect mitochondria are their low stability, their exceptionally high respiratory and phosphorylative activity with their physiological substrates, their relatively poor rate of oxidation of Krebs-cycle intermediates and the low P:0 ratios accompanying these slow oxidations. The phosphorylating respiratory chain of insect mitochondria strongly resembles that of mammalian mitochondria [106]. The electron transport chain is a mitochondrial pathway in which electrons move across a redox span of 1.1 V from NAD/NADH to O_2/H_2O. Three complexes are involved in this chain, namely, complex I, complex III, and complex IV. Some compounds like succinate, which have more positive redox potential than NAD/NADH, can transfer electrons via a different complex—complex II (**Figure 29**) [107].

6.1 Compounds acting *via* electron transport chain

- Cyazofamid

Cyazofamid is a cyanoimidazole fungicide particularly effective on *Oomycota*. This molecule, inspired in natural imidazoles, inhibits ATP production in cells by

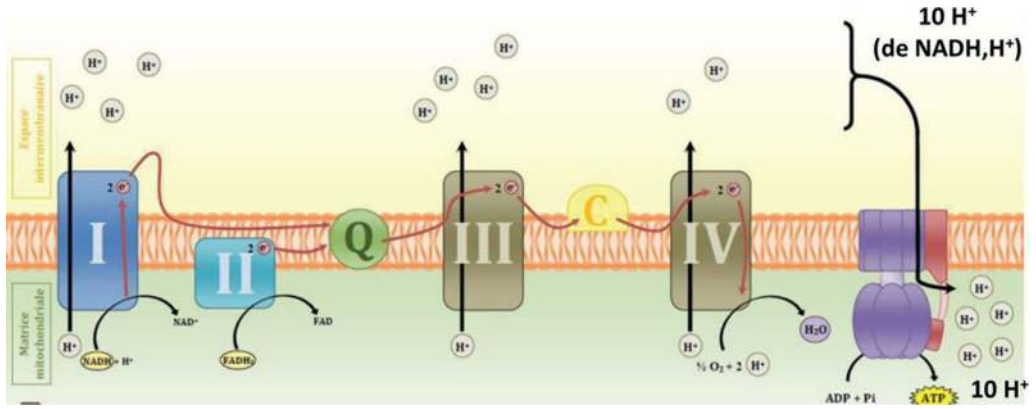


Figure 29.
Electron transport chain [108].

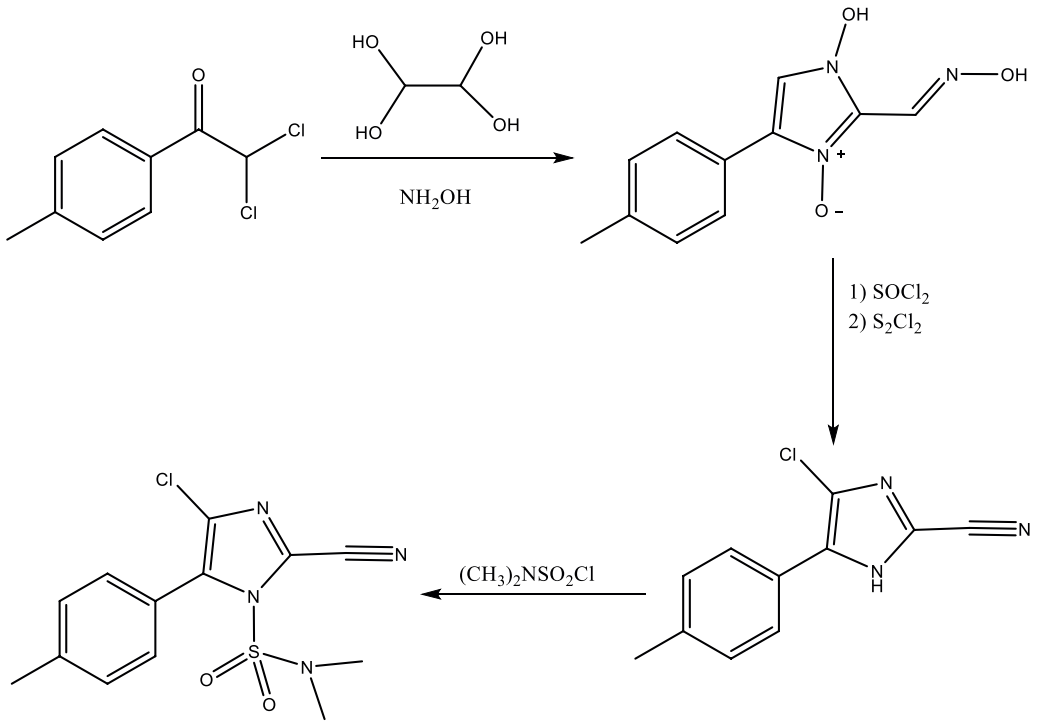


Figure 30.
Cyazofamid synthesis.

inhibiting the complex III of the respiratory chain of the mitochondria [84]. It is a synthetic fungicide whose synthesis is described as follows; an acetophenone derivative was treated with aqueous glyoxal and hydroxylamine to form an oxime substituted imidazole ring system. This intermediate was treated with thionyl chloride and disulfide dichloride to convert the oxime to a cyano group chlorinating the imidazole in the position near the phenyl ring. Finally, treatment with dimethylsulfamoyl chloride gave cyazofamide (**Figure 30**).

7. Conclusion

In summary, pesticides are a major environmental issue. Alternative strategies need to be explored, based on phytocompounds and natural extracts. Following this idea, the synthetic compounds mimicking the structure of natural products and modifying this molecules by several approaches as for example hemisynthesis or total synthesis will enhance the molecular diversity. These innovative biomimetic modified pesticides will open new perspectives in the fight against pests, improving crop efficiency and decreasing food crisis while maintaining sustainability.

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