Agrochemicals for Sustainability in Agriculture

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Edited by

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PREFACE

Agriculture stands at a pivotal crossroads in the 21st century. As global populations surge and natural resources dwindle, the demand for sustainable food production has never been more urgent. In this challenging landscape, agrochemicals—encompassing pesticides, growth regulators, food additives—have emerged as vital tools in the pursuit of enhanced agricultural productivity. Yet, their use raises important questions about environmental integrity, human health, and long-term sustainability.

This book, *Agrochemicals for Sustainability in Agriculture*, seeks to offer a comprehensive and balanced exploration of the role agrochemicals play in shaping modern agricultural practices. It delves into the scientific, environmental, and socio-economic aspects of agrochemical usage, aiming to bridge the gap between productivity and sustainability.

Our objective is not merely to advocate for or against agrochemicals, but to evaluate their potential within a framework of responsible use, regulatory oversight, and integrated approaches including integrated pest management (IPM). By examining case studies, current research, and global trends, this volume hopes to contribute meaningfully to the ongoing discourse on sustainable agriculture.

The book deals with the newer pesticide molecules especially insecticides, fungicides, herbicides and nematicides and their mode of action. It also describes the plant growth regulators and food additives used during production and processing of foods. One of the chapter is devoted to the management of storage pests, which is otherwise not addressed properly. Fate of pesticides in the environment is also described in details, which is important in the context of sustainability. Residual status of pesticides in fruits and vegetables was also discussed in the Indian context for the understanding of the readers.

This book is intended for a wide audience—agricultural scientists, environmentalists, policymakers, students, and practitioners—who are invested in finding innovative and pragmatic solutions to feed a growing world while preserving the ecosystems on which we all depend.

We hope this book contributes meaningfully to the ongoing global dialogue on food security, environmental protection, and agricultural innovation—fostering interdisciplinary collaboration and paving the way for a more resilient and sustainable agricultural future.

Supradip Saha
Aditi Kundu

CHAPTER 1

NEW GENERATION INSECTICIDES FOR INSECT PEST MANAGEMENT

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Abstract

Time involved in the discovery of new insecticidal molecule from start of a research effort around an area of chemistry, to the synthesis and characterization of the molecule to develop a suitable formulation product is considered very high. It is estimated that at least 8 to 12 years required for recognizing a chemical structure for insecticide development starting from identification through development and registration process is highly costly affair. Most commonly, the discovery process requires several years of effort. Perhaps not surprisingly, there may be a sense that insecticide discovery is getting more difficult; that it was easier, and took less time and effort in the past than it does today. While the time needed to fulfill regulatory aspects has certainly gotten longer over the years. Research is growing immensely to develop insecticides with multidimensional functional properties targeting multiple sites in insect pests. Agrochemical industries are coming with newer insecticidal molecules with novel mechanism of actions which can tackle the issues of resistance and resurgence problems. This chapter describes some of these newer insecticides introduced recently for agricultural insect pest control.

Key words Insects, mites, Mode of action, Sucking pest, Chewing pest, IRAC

Abbreviations

IRAC	Insecticide Resistance Action Committee
OPs	Organophosphorus insecticides
MoA	Mode of action
nAChR	Nicotinic Acetylcholine Receptor
TRPV	Transient Receptor Potential Vanilloid (a type of ion channel)
GABA	γ-Aminobutyric acid
CO-NIs	Chordotonal Organ Nicotinamidase Inhibitors
PPCs	Pyrazolecarboxamides
CNS	Central Nervous System

1.1 Introduction

Biotic stress is a major factor in the global decline in crop productivity. In agricultural systems, one of the main factors causing harm to crop production and storage is insects. These pests are thought to be responsible for losses of about 60-70% in tropical nations, mostly in stored goods (Thomas 1999). Given that they outnumber all other animal groups in terms of total population, insects are without a doubt the most adaptable form of life. Most insects have direct benefits for both the environment and people. Insects cause harm to people, livestock, and crops (Williams 1947). Global crop losses continue to be a concern even with the annual US $35,000 spent on applying one million metric tons of pesticides and the use of numerous biological and other non-chemical controls worldwide (Pimentel 2007). Around the world, a wide range of insect pests and disease vectors have been controlled since the discovery of the first truly effective synthetic organic insecticides, such as 1,1,1-trichloro-2,2-bis(p-chlorophenyl) ethane (DDT), cyclodienes, organophosphorus insecticides (OPs), and later N-methyl carbamates. These early synthetic organic insecticidal chemicals also brought to light several significant toxicological and environmental problems, as well as worries about the characteristics and application of pesticides (Jeschke, 2017). Apart from these negative environmental aspects, nowadays there are populations of insects which are resistant to organochlorine, organophosphorus and carbamate insecticides. This marked the start of the protracted search for novel insecticidal chemicals that could satisfy the ever-changing and stricter specifications concerning the effects on the environment, toxicological profiles, and consumer demands (Singh et al. 2019). Affordability and efficacy against a variety of insect pests, including those that are resistant to current insecticides, must be combined with the increasingly stringent regulatory requirements.

Insecticides are widely used globally to mitigate insect destruction of crops, structures, and stored products, and to protect humans and domesticated animals from arthropod parasites. The Insecticide Resistance Action Committee (IRAC), a global technical working group of insecticide industry experts, publishes the authoritative classification of insecticides based on mode of action. Although there are currently 32 mode of action groups in the classification, as well as several insecticides with unknown modes of action, some pest insects have developed resistance to most existing insecticides and are difficult or impossible to control, emphasizing a need for novel insecticide modes of action to control these highly resistant insects. Moreover, one of the most effective means available to minimize selection for resistance is to rotate insecticides with different modes of action, so new modes of action are also important for preserving the utility of existing ones.

The importance of controlling pests has led to the development of a variety of insecticides that prevent agriculture losses. Toxicological studies based on acute and chronic effects upon exposure have revealed that many classical insecticides are highly toxic not only to non-targeted insect species, but also to living organisms. Furthermore, some of them have proved to cause cumulative effects on long-term exposure. Implementation of strict regulatory controls by the authorities throughout the world resulted restriction or even banned of use of many classical insecticides belonging to organochlorinated hydrocarbons and organophosphorus and carbamate compounds (Hummel 1983). In order to overcome ecological toxicity and human health issues including increasing resistance problems of the pests due to upcoming climate changes, it would be interesting to have new insecticides with novel mechanisms of action (Sparks and Bryant 2022). These above-mentioned factors have a significant impact on the agrochemical industries, particularly involved in finding and creating new insecticides (Oberemok et al. 2015). Indeed, search for safer alternatives for pest control is the need of the hour. Thus, intense research is being carried out to obtain chemically-modified substances with improved insecticidal activity in terms of selectivity towards insects and low toxicity to the environment, and to non-targeted species including humans (Allossogbe et al. 2017). The combination of new synthetic approaches and biological and physiological studies has resulted in the preparation of insecticides with a better environmental profile, with different mechanisms of actions, and with reduced risks for living systems. This quest for new insecticidal chemistries has resulted in an array of different classes of chemistries discovered and developed over the past eight decades. Importantly, many of these classes possess novel modes of action (MoA) (Sparks et al. 2022) and described in Table 1.1.

Table 1.1 Development of new insecticides for plant disease management.

Active ingredient	MOA	IRAC class	Effective against
Flupyrimin	Nicotinic acetylcholine receptor (nAChR) competitive modulators	4	*Plutella xylostella, Nilaparvata lugens, Nephotettix nigropictus*
Sulfoxaflor	Nicotinic acetylcholine receptor (nAChR) competitive modulators	4	Sap feeding insects
Flupyradifurone	Nicotinic acetylcholine receptor (nAChR) competitive modulators	4	*Bemisia tabaci, Scirtothrips dorsalis, Planococcus citri*
Triflumezopyrin	Nicotinic acetylcholine receptor (nAChR) competitive modulators	4	*Nilaparvata lugens, Sogatella furcifera*
Pyrifluquinazon	Chordotonal organ TRPV channel modulators	9	*Bemisia tabaci, Scirtothrips dorsalis, Planococcus citri*
Afidopyropen	Chordotonal organ TRPV channel modulators	9	*Bemisia tabaci* and other Sucking pests
Flonicamid	Chordotonal organ TRPV channel modulators-Unidentified target	29	Sucking pests

Dimpropyridaz	Chordotonal organ modulators – undefined target site	36	*Bemisia tabaci, Trialeurodes* spp, *Brevicorvne brassicae*
Spiropidion	Inhibitors of acetyl CoA carboxylase	23	-
Flubendiamide	Ryanodine receptor modulators	28	*Cnaphalocrocis medinalis, Scirpophaga incertulas*
Chlorantraniliprole	Ryanodine receptor modulators	28	*Helicoverpa armigera Earias vittela*
Cyantraniliprole	Ryanodine receptor modulators	28	-
Tetraniliprole	Ryanodine receptor modulators	28	*Carpophilus lugubris, Anthonomus pomorum, Naupactus cervinus*
Cyclaniliprole	Ryanodine receptor modulators	28	-
Broflanilide	GABA-gated chloride channel allosteric modulators	30	*Plutella xylostella, Spodoptora frugiperda, Thrips tabaci*
Isocycloseram	GABA-gated chloride channel allosteric modulators	30	Lepidopteran, Hemipteran, Coleopteran, Thysanopteran and Dipteran pest species

Fluxametamide	GABA-gated chloride channel allosteric modulators	30	*Plutella xylostella, Leucinodes orbonalis, Spodoptera litura*
Acynonapyr	Calcium-activated potassium channel (KCa_2) modulators	33	*Tetranychus urticae, Panonychus citri*
Flometoquin	Mitochondrial complex III electron transport inhibitors – Qi site	34	*P. xylostella, S. litura*

1.2 Nicotinic Acetylcholine Receptor (nAChR) Competitive Modulators

Nicotinic acetylcholine receptor (nAChR) competitive modulators are insecticides that target the nervous system of insects. These modulators interfere with the binding of acetylcholine to nAChRs, preventing the transmission of nerve signals. By competitively binding to nAChRs, they block the action of acetylcholine, a neurotransmitter essential for normal nerve function. This interference disrupts synaptic transmission, leading to paralysis and eventual death of the insect. Because nAChRs are ubiquitous in the nervous system of insects, these modulators are effective against a wide range of pest species, including insects resistant to other classes of insecticides. However, continuous exposure to nAChR modulators can lead to the development of resistance in insect populations. Therefore, it is essential to rotate insecticides with different modes of action and incorporate integrated pest management strategies to mitigate resistance and maintain their effectiveness in pest control. Recently, flupyrimin, sulfoxaflor, flupyradifurone, triflumezopyrin and dicloromezotiaz have been discovered and marketed (Fig. 1.1).

1.2.1 Flupyrimin

This insecticide belongs to pyridinylmethylidene pyridylacetamide class, developed by Meiji Seika Pharma, registered in the year 2018 (USA). Primarily targets sucking insects like aphids, whiteflies, brown planthoppers, leafhoppers, and planthoppers. Effective against some chewing insects like thrips and diamondback moth larvae as well (Onozaki et al. 2017). This pesticide is especially effective against rice pests resistant to imidacloprid with superior safety toward pollinators. In market, it is available in the name of Viola, Imagine. For BPH control in rice field, the recommended dose is 400 mL/acre. Flupyrimin is persistent, stable to the environment, and has a hydrolysis half-life of 228 days (25 °C, pH 7), which may pose a risk to surface water and ecosystems (Zhao et al. 2022).

1.2.2 Sulfoxaflor

A pyridine and a trifluoromethyl compound, it is a member of a class of chemicals called sulfoximines. It was registered in 2017. Sulfoxaflor is a systemic insecticide and kills through contact or ingestion (Babcock et al. 2011). There has been some debate over sulfoxaflor's possible effects on pollinators, especially bees. It works well against pests that are developing resistance to insecticides such as pyrethroid, carbamate, neonicotinoid, and organophosphate. Sulfoxaflor is an important and highly effective tool for growers that targets difficult pests such as aphids and tarnished plant bugs (Zhu et al. 2011).

It acts in a novel way on the central nervous system of insects, such as aphids which have developed resistance to other pesticides and targets the insect nicotinic acetylcholine receptor. It exhibits a high degree of efficacy against a wide range of sap-feeding insects, including those resistant to neonicotinoids and other insecticides. However, since several years, there are some studies that reported that the sulfoximine insecticides could also represent a risk for pollinators (Watson et al. 2021). It is used as foliar spraying treatments on fruiting vegetables, spring and winter cereals and cotton to control sap feeding insects. It breaks down quickly in soil but is highly persistent in water, with a half-life of 37 days to more than a year.

1.2.3 Flupyradifurone

This is a systemic butenolide insecticide developed by Bayer Crop Science under the name Sivanto®. It is registered in the year 2015. It is an agonist of insect nicotinic acetylcholine receptors. It primarily targets sap-feeding pests like aphids, whiteflies, mealybugs, leaf miners, and scales. Also effective against certain hoppers and plant bugs thereby maintaining yields of crops such as vegetables, fruits, cotton, and coffee. Formulations available as soluble liquids and flowable concentrates. Application methods are foliar spray, soil drench and seed treatment.

1.2.4 Triflumezopyrin

This novel insecticide works by binding to the orthosteric site of the nicotinic acetylcholine receptor through competitive binding, which causes the insects to become lethargic and poisoned. It has been shown to be highly effective in controlling both imidacloprid-susceptible and imidacloprid-resistant insects. It belongs to the mesoionic class of chemicals. It was first commercialized in 2012 by DuPont and is now used in a number of countries around the world, including India. Triflumezopyrim is primarily used to control hoppers, such as the brown planthopper (*Nilaparvata lugens*) and the white-backed planthopper (*Sogatella furcifera*). In terms of beneficial insects, like parasitoids and predators, it is comparatively non-toxic. In rice fields, this may aid in the preservation of beneficial insects. Although some aquatic species find it toxic.

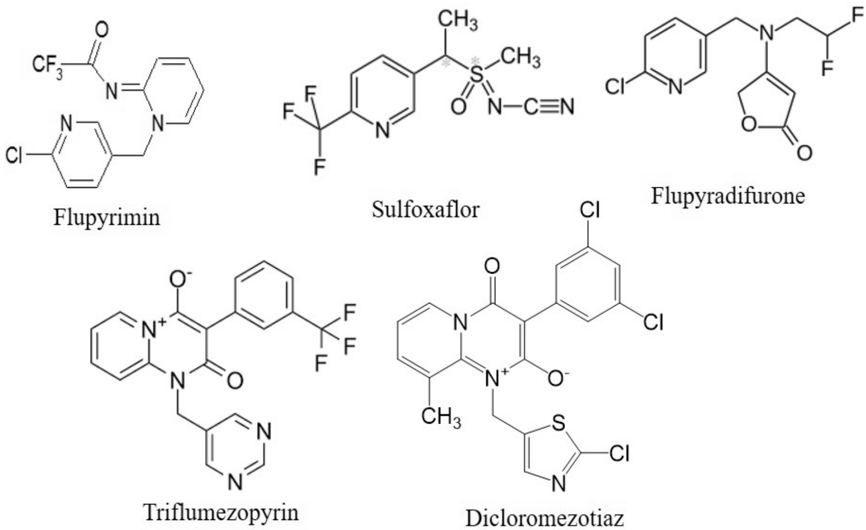


Fig. 1.1. Recent introduction of insecticides as nicotinic acetylcholine receptor competitive modulators.

1.2.4 Dicloromezotiaz

Dicloromezotiaz is a mesoionic thiazolo-pyridopyrimidine insecticide belong to organochlorine insecticide, highly effective against rice hoppers. Dicloromezotiaz is a product of ZM Crop Protection Corporation, considered safe to mammals and environment. It is an antagonist of insect nAChR channel. It is recommended for the management of lepidopteran pests and functions at the orthosteric-binding nAChR, rarely studied mechanism of action for the Lepidopteran insects (Holyoke et al. 2017). It also shows excellent efficacy to Coleopteran pest and termites including those developed resistance against other commonly used insecticides. Innovative transmitting efficacy of the insecticide is commendable for termite control.

1.3 Chordotonal Organ TRPV Channel Modulators

Chordotonal organ nicotinamidase inhibitors (CO-NIs) are a class of insecticides that disrupt the function of chordotonal stretch receptor organs in insects. These organs are responsible for sensing gravity, balance, acceleration, hearing, proprioception, and kinesthesia. Disrupting these organs affects an insect's behavior and feeding. Chordotonal organs are important mechanosensors in insects and crustaceans, transducing joint position and motion due to muscle contractions, or external stimuli such as wind, gravity or sound, and are, therefore, essential for hearing, balance, spatial orientation and kinesthesia senses. Disrupting these important senses impacts behavior in specific ways that are devastating to the survival of certain insects but might not be obvious to the casual observer. The first chordotonal organ disruptor insecticide, pymetrozines (introduced in 1994 by Ciba-Geigy) was called a selective homopteran feeding blocker because it was selective for sucking insects, especially aphids, and was specifically disrupt their ability to feed.

Newly introduced insecticidal molecules namely, pyrifluquinazon, afidopyropen, dimpropyridaz and flonicamid (Fig. 1.2) bind to and disrupt the gating of Nan-Iav TRPV (Transient Receptor Potential Vanilloid) channel complexes in chordotonal stretch receptor organs, which are critical for the senses of hearing, gravity, balance, acceleration, proprioception, and kinesthesia. This disrupts feeding and other behaviors in target insects (Spalthoff et al. 2023).

1.3.1 Pyrifluquinazon

It is a broad-spectrum insecticide that is effective against a variety of sucking insect pests, including whiteflies, aphids, psyllids, and mealybugs. It is developed by Nichino/Nihon Nohyaku Co., Japan. This systemic insecticide works by disrupting the insect's nervous system, causing it to stop feeding and die. In India, it is marketed by TATA Rallis in the name of

'Clasto' (Pyrifluquinazon 20% WG). Pyrifluquinazon acts *via* contact and ingestion and belongs to IRAC group 9B. A wide variety of agricultural uses (>100 different crops) including vegetables, tree fruits, grapes, other fruits, tree nuts, potatoes, and cotton. Other uses include nursery uses.

1.3.2 Afidopyropen

Afidopyropen, a novel insecticide, is a derivative of pyripyropene A, which is produced by the filamentous fungus *Penicillium coprobium.* It is a foliar insecticide that functions by disrupting feeding and other behaviors in target insects. It modulates chordotonal organs of American grasshoppers (*Schistocerca americana*) (Kandasamy et al. 2017). Afidopyropen stimulated heterologously expressed TRPV channels from two different insect species - fruit fly (*Drosophila melanogaster*) and pea aphid (*Acyrthosiphon pisum*) - but did not affect function of the mammalian TRPV channel TRPV4. It is effective against sucking insects such as aphids, spider mites, whitefly, thrips, psyllids, mealybugs, scale in vegetables, fruit, nuts, cotton, ornamentals. It is moderately persistent in soil and water. It is moderately mobile and may leach to groundwaters. It has a favorable biodiversity toxicity profile including its impact on bees. It has a low oral toxicity to mammals.

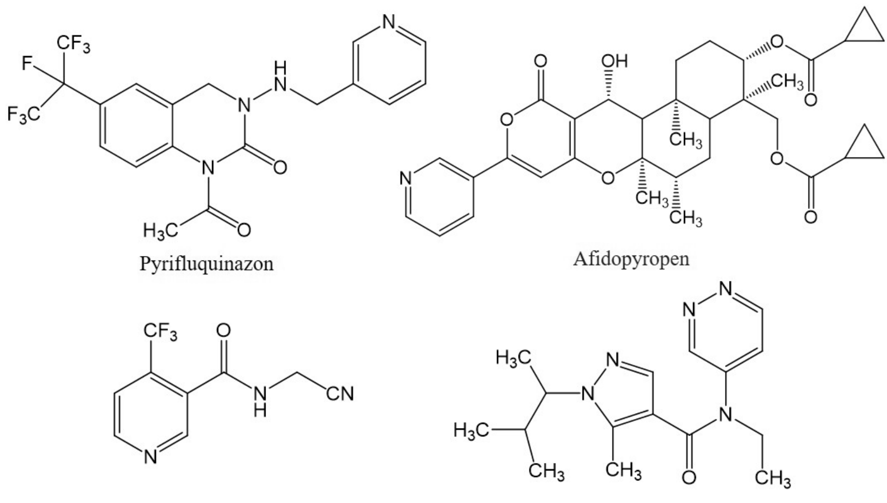


Fig 1.2. Recent introduction of insecticides as chordotonal organ TRPV channel modulators.

1.3.3 Flonicamid

Flonicamid (IKI-220; N-cyanomethyl-4-trifluoromethylnicotinamide), a selective insecticide discovered by Ishihara Sangyo Kaisha, Ltd and developed jointly with FMC Corporation, was launched in 2005 and is currently registered in more than 40 countries for the control of a broad range of aphid pests as well as some other hemipteran and Thysanopteran pests (Morita et al. 2007). Flonicamid is a proinsecticide whose bioactive metabolite 4-trifluoromethlynicotinamide (TFNA-AM) disrupts chordotonal organ function in a way that is indistinguishable from the Group 9 insecticide pymetrozine, but it does not affect the function of TRPV channels in heterologous systems or the binding of [3 H]-afidopyropen to TRPV channels, and has therefore, been classified by IRAC into Group 29, chordotonal organ modulators—undefined target site. It has been found to block Kir channels, but it is not known whether TFNA-AM has this effect or whether Kir channels play a role in chordotonal organ function (Taylor-Wells et al. 2018).

1.3.4 Dimpropyridaz

Dimpropyridaz is being developed by BASF as the first pyridazine pyrazolecarboxamides (PPC), a novel insecticide class discovered through *in vivo* screening and optimized at BASF. It is a pro-insecticide used to control sucking and chewing insect pests particularly, aphid species as well as whiteflies and other piercing–sucking insects (Shang et al. 2023). It is mainly used in cotton and vegetables for controlling of silver leaf whitefly (*Bemisia tabaci*), greenhouse whitefly (*Trialeurodes spp*), cotton/melon aphid (*Aphis gossypii*), cabbage aphid (*Brevicoryne brassicae*). In market sold in the name of Efficon®, registered in the year 2022.

PPCs are a new class of chordotonal organ modulator insecticide with a mode of action that is different from IRAC groups 9 and 29. Active secondary amide metabolites of PPCs potently inhibit the function of insect chordotonal neurons (Chen et al. 2022). Unlike Group 9 and 29 insecticides, which hyperactivate chordotonal neurons and increase Ca^{2+} levels, active metabolites of PPCs silence chordotonal neurons and decrease intracellular Ca^{2+} levels. Whereas the effects of Group 9 and 29 insecticides require TRPV (Transient Receptor Potential Vanilloid) channels, PPCs act in a TRPV-independent fashion, without compromising cellular responses to Group 9 and 29 insecticides, placing the molecular PPC target upstream of TRPVs (Spalthoff et al. 2023).

1.4 Inhibitors of Acetyl CoA Carboxylase

Insecticides based on inhibitors of acetyl-CoA carboxylase (ACC) disrupt lipid metabolism in insects. ACC is a key enzyme involved in fatty acid synthesis, catalyzing the carboxylation of acetyl-CoA to malonyl-CoA, a precursor in fatty acid biosynthesis. Inhibitors block this enzymatic activity, leading to a reduction in malonyl-CoA levels and subsequently inhibiting fatty acid synthesis. As lipids are essential for membrane integrity, energy storage, and various other physiological processes such as disruption of lipid metabolism impairs insect growth, development, reproduction etc. Furthermore, the reduction in lipid reserves may lead to energy depletion and eventual mortality. Insecticides targeting ACC offer a selective approach to pest control with minimal impact on non-target organisms (Lümmen et al. 2014). However, continuous monitoring for resistance development is crucial. Overall, by disrupting lipid metabolism, ACC inhibitors-based insecticides provide an effective strategy for managing insect populations and mitigating crop damage. Insecticides of the tetronic/tetramic acid group or cyclic ketoenols are known inhibitors of acetyl CoA carboxylase particularly highly effective against sucking pests such as whiteflies, aphids and mites. They act as inhibitors of acetyl-CoA carboxylase, a key enzyme required for lipid biosynthesis across taxa.

Insecticides belong to cyclic ketoenols, such as spirotetramat-enol is used to control sucking pests like aphids, mites, and whiteflies. Some of the newly introduced insecticides under this class are spirodiclofen, spiropidion, spirotetramat, spidoxamat including spiromesifen. Molecules from aryloxyphenoxypropionate (FOPs), cyclohexanedione (DIMs), and phenylpyrazolin are well known herbicides, inhibit the acetyl-CoA carboxylase protein particularly catalyze the first step in fatty acid synthesis.

1.4.1 Spirotetramat

Spirotetramat is a quaternary ketone acid compound belonging to the class of cyclic keto-enols (under IRAC group 23). It is a new insecticide and acaricide, developed by Bayer Crop Science. It is hydrolyzed to the corresponding spirotetramat-enol, the presumed active form of spirotetramat in plants. It has shown outstanding performance against sucking insect pests in laboratory and greenhouse assays as well as in semi-field and field trials. It acts as an inhibitor of lipid biosynthesis and controls juvenile stages, with additional effects on adult fecundity (Brück et al., 2009). It also affects the embryonic process. It is marketed with the trade name Movento® and Ultor®.

1.4.2 Spirodiclofen

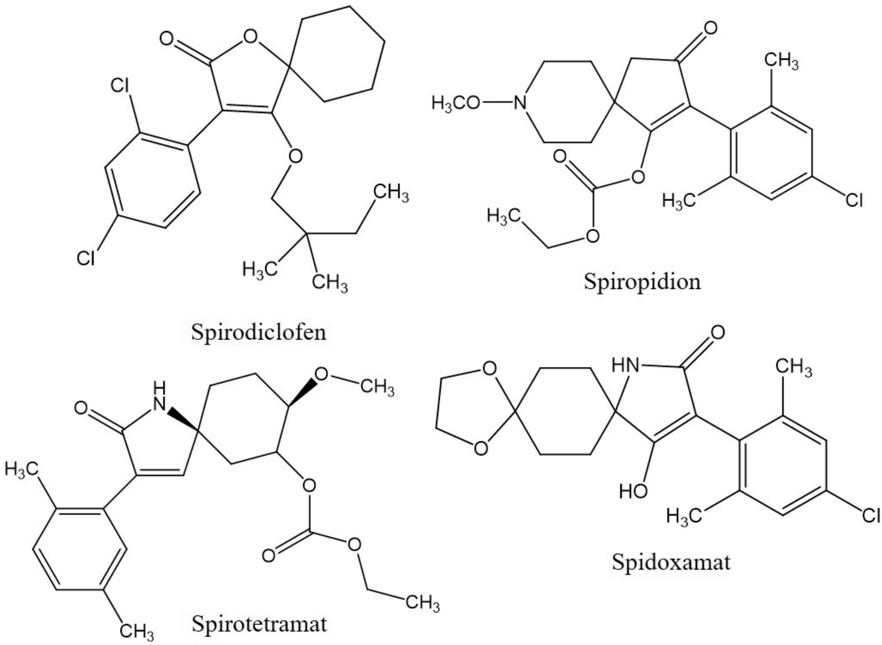


Fig 1.3. Recent introduction of insecticides as inhibitors of acetyl CoA carboxylase.

Spirodiclofen is a tetronic acid derivatives with acaricidal action. It acts by interfering with mite development, thereby controlling such pests as *Panonychus* spp., *Phyllocoptruta* spp., *Brevipalpus* spp., *Aculus* and *Tetranychus* species. It is active by contact action to mite eggs, all nymphal stages, and adult females (adult males are not affected). Spirodiclofen is structurally similar to spiromesifen, which is also a tetronic acid insecticide. It is a selective, non-systemic foliar insecticide and acaricide belonging to the chemical class of ketoenols or tetronic acids with the mode of action of lipid biosynthesis inhibition (Fig. 1.3). It is marketed under global trade name Envidor® /Japan Daniemon 1,2®. It shows no cross-resistance to currently available acaricides including hexythiazox, clofentezine, mitochondrial electron transport inhibitors (e.g. pyridaben), abamectin and others. Its broad spectrum of activity, excellent long-lasting efficacy, good plant compatibility in all relevant crops and lack of cross-resistance make spirodiclofen an excellent com pound for the use in the most important markets for specific acaricides.

1.4.3 Spiropidion

It is an insecticide (Fig. 1.3) of the tetramic acid family. It is capable of controlling a broad range of sucking pests, e.g. aphids, whiteflies, psyllids, scales and mites, on vegetables and specialty crops. It is ideal for Integrated Pest Management (IPM) techniques because it is safe for pollinators and other non-target organisms. Spiropidion was announced by Syngenta Crop Protection as a new insecticide in 2017 (Mahdavi et al. 2023). Guatemala obtained the first worldwide registration of a product formulated with spiropidion in September 2020, where the product will be marketed under the brand name ELESTAL® Neo.

Spiropidion is considered as a proinsecticide, which after application hydrolyses to releases its bioactive active ingredient, 2-aryl-cyclic-1,3-dione moiety that undergoes keto-enol tautomerism mechanism to get the stable conformation before inhibiting the target site of the proteins in insects. It is an acetyl-CoA carboxylase inhibitor, can easily able to disrupt fatty acid biosynthesis process. Physico-chemical properties of the molecule indicates its weak acidic character, water solubility and lipophilicity. The two-way systemicity of 2-aryl-cyclic-1,3-dione moiety allows its translocation to the new growth, providing holistic whole plant protection from the sucking pests. It is safe for the environment, pollinators and other nontarget organisms. Researchers has already considered the molecule perfectly suitable for IPM practices (Muehlebach et al. 2021).

1.4.4 Spidoxamat

It is a novel ketoenol insecticide with both foliar and soil applications. It is a tetramic acid insecticide introduced by Bayer Crop Science, known to inhibit acetyl CoA carboxylase protein. Generally used for the management of sucking pests in soybeans, cotton, fruit, vegetables.

1.5 Ryanodine Receptor Modulators

Numerous biological processes, such as the contraction of muscles and the release of neurotransmitters, depend on calcium (Ca^{2+}). When the calcium channels are normally activated, calcium ions flow into muscle fibers, thus stimulating contraction. The ryanodine receptors (or channels) are responsible for regulating the release of internal calcium stores into the cytoplasm of insects and mammals.

The anthranilic diamide or ryanodine receptor modulator insecticides (Fig. 1.4) work by binding to and activating the ryanodine receptors, causing the calcium channels to remain partially open, resulting in excessive and uncontrollable release of stored calcium ions into the muscles. Consequently, the release of calcium ions into the muscles disrupts normal functioning; thus, leading to muscular contractions, paralysis and eventually death.

1.5.1 Flubendamide

This systemic insecticide is developed by Nihon Nohyaku Co., Ltd and registered in the year 2007. The ryanoid class chemical contains a perfluorinated functional group. Primarily manages stem borer, leaf folder in rice, fruit borer in chili, fruit and shoot borer in brinjal, diamond black moth in cabbage etc. From 2008 to 2016, in US the product was registered for restricted use, but the manufacturers voluntarily canceled because of its environmental concerns but the product is available in other regions, including India and Europe. Available as water dispersible granules, soluble liquids and suspension concentrates. In market sold in the name of Fame®, Takibi®, Fluben®.

1.5.2 Chlorantraniliprole

This insecticide belongs to the anthranilic diamide class, known for its unique mode of action and selective targeting. It is developed by DuPont company and registered in the year 2009. It is used to control gram pod borer, pod fly in pigeon pea, pod borer in black gram, American boll worm, spotted boll worm and tobacco caterpillars in cotton, diamond black moth in cabbage, termite early shoot and top borer in sugarcane etc. In market available in the name of Shimo®, Citigen®, Starc®, Coragen® etc.

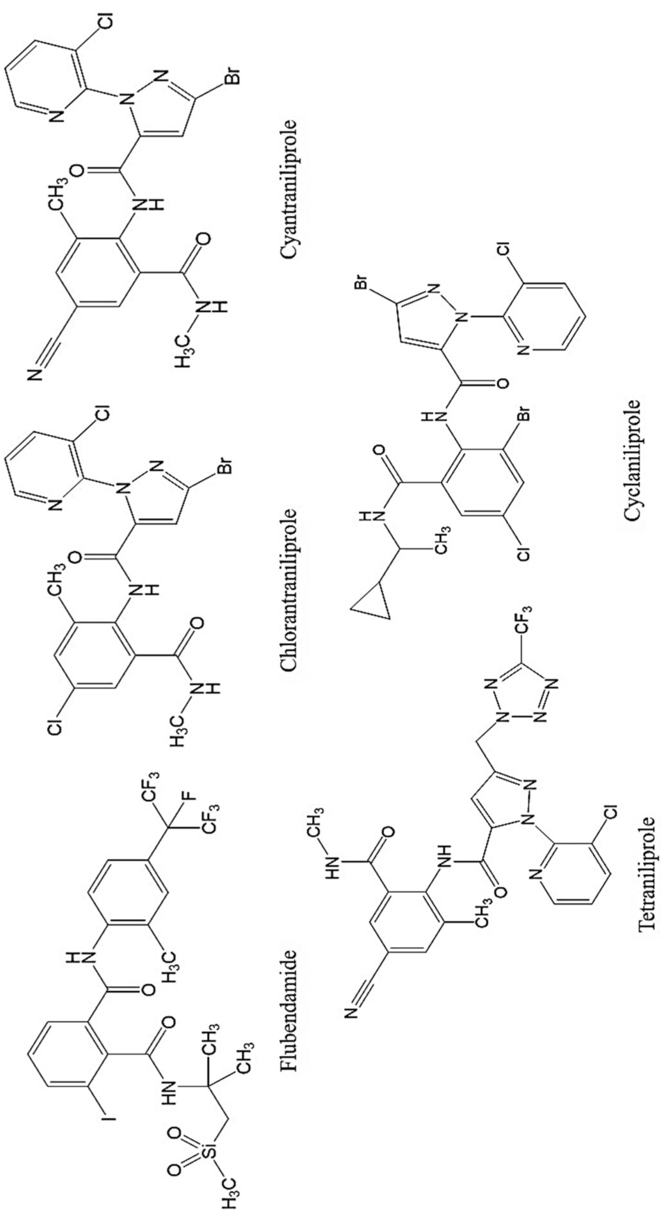


Fig. 1.4. Recent introduction of insecticides as ryanodine receptor modulators.

1.5.3 Cyantraniliprole

It is an anthranilic diamide insecticide in the form of an oil dispersion formulation designed for foliar spray. It is developed by DuPont company and registered in 2014. A crop that receives this insecticide early in its life cycle has a more promising start and early crop establishment, which opens the door to a higher yield and improved crop quality. This insecticide is used in capsicum, tomato, cucurbits, eggplants for controlling sucking and chewing insects. It is marketed in the name of Benevia® by FMC.

1.5.4 Tetraniliprole

It is a carboxamide that is cyantraniliprole in which the bromine atom has been replaced by a [5-(trifluoromethyl)-2H-tetrazol-2-yl]-methyl group. Developed by Bayer Crop Science and sold in the name of Vayego®. It is a powerful, innovative insecticide that provides quick antifeedant and residual activity on all life stages from egg to adult on a broad spectrum of pests. The quick feeding cessation minimizes potential fruit damage in pome fruit, stone fruit and almond crops and has proven efficacy on key pests such as codling moth, light brown apple moth, oriental fruit moth, Carpophilus beetle, garden weevil, Fuller's rose weevil and apple weevil.

1.5.5 Cyclaniliprole

This diamide insecticide is discovered by ISK and registered in the year 2017. It is a racemic mixture (R and S enantiomers present in a 50:50 w/w ratio). With its combination of good rainfastness and long-lasting efficacy the use of cyclaniliprole will reduce the number of required applications. In addition to its outstanding efficacy, cyclaniliprole has excellent crop safety for all registered crops. It is highly effective against numerous insect pest in various orders, including Lepidoptera, Coleoptera, Hemiptera, Thysanoptera and Diptera.

1.6 GABA-Gated Chloride Channel Allosteric Modulators

Insects, like humans, have a nervous system that relies on neurotransmitters to send signals. γ-aminobutyric acid (GABA) is the major inhibitory transmitter controlling synaptic transmission and neuronal excitability. It is present in a high percentage of neurons in the central nervous system (CNS) and also present in the peripheral nervous system, and acts to maintain a balance between excitation and inhibition (Solomon et al. 2019). It binds to

GABA-gated chloride channels, which are protein structures embedded in the cell membrane. When GABA binds, these channels open, allowing negatively charged chloride ions to flow into the nerve cell. This influx of chloride ions makes the inside of the cell more negative, making it harder for the cell to send electrical signals (action potentials). GABA-gated chloride channel allosteric modulators (Fig. 1.5) are a type of insecticide that target these channels but don't directly mimic GABA itself. Instead, they bind to a different site on the channel, acting like a switch.

1.6.1 Fluxametamide

This isoxazoline insecticide was discovered and synthesized by Nissan Chemical Industries, Ltd. It is registered in the year 2019. Shows good activity against leaf hopper, thrips, fruit and shoot borer of eggplants, diamondback moth of cabbage, thrips, fruit borer, tobacco caterpillar of chili, leaf hopper, thrips, fruit borer of okra, spotted pod borer of red gram, pod borer, thrips, fruit borer of tomato. Commercially available in the form of 10% EC- Gracia®.

1.6.2 Broflanilide

It is developed by Mitsui Chemicals. Registered in USA and Canada in 2021. Insecticide has a unique chemical structure characterized as a meta-diamide. A valuable and important aspect of Broflanilide is its ability to move across leaf tissue after a foliar application (from one side of the leaf to the other), known as translaminar movement, ensuring that the active ingredient moves throughout insect-feeding areas. It has strong broad-spectrum efficacy and can be applied in a range of ways, including: foliar, in-furrow and seed treatment for the control of tough chewing insects and soil dwelling pests, like *Plutella xylostella, Spodoptora frugiperda, Thrips tabaci, Liriomyza sativae, Leucoptera coffeella* etc. as well as urban and rural pests such as termites, ants, cockroaches and flies. Marketed by BASF in the name of Exponus®. The EPA has stated that Broflanilide is "Likely to be Carcinogenic to Humans"

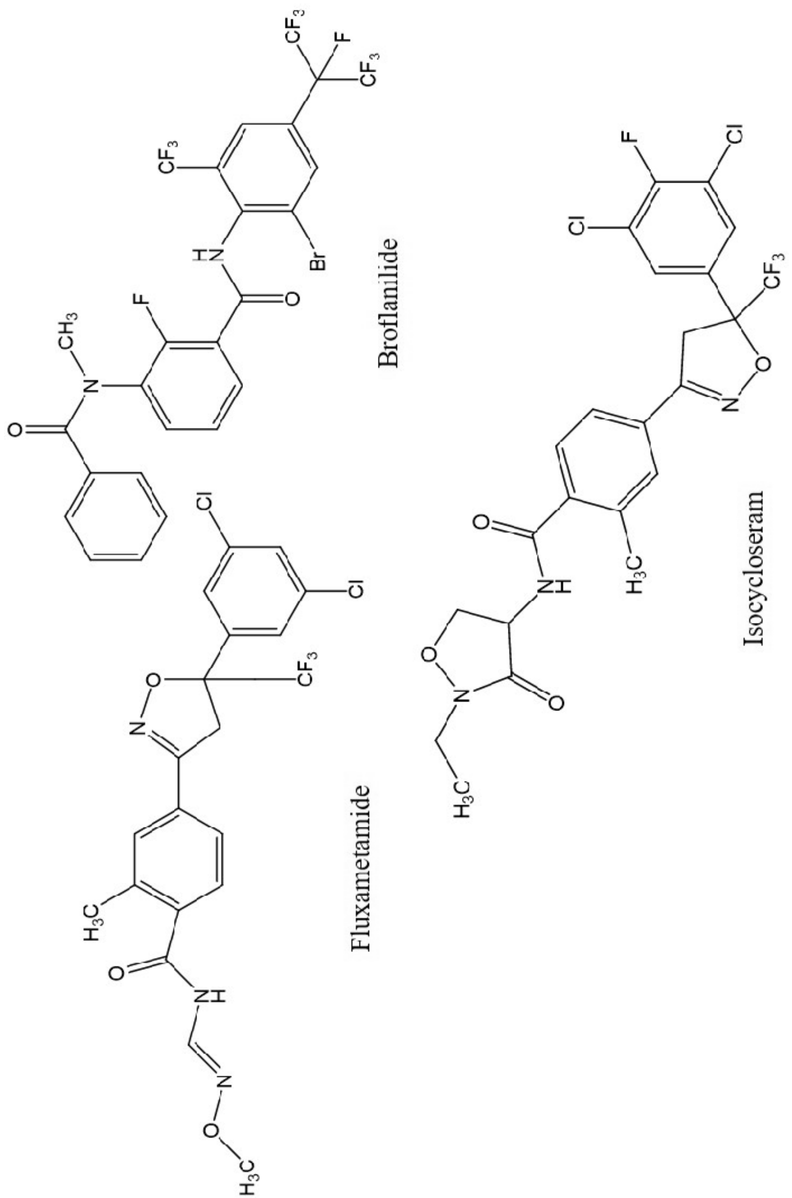


Fig 1.5. Recent introduction of insecticides as GABA-gated chloride channel allosteric modulators.

1.6.3 Isocycloseram

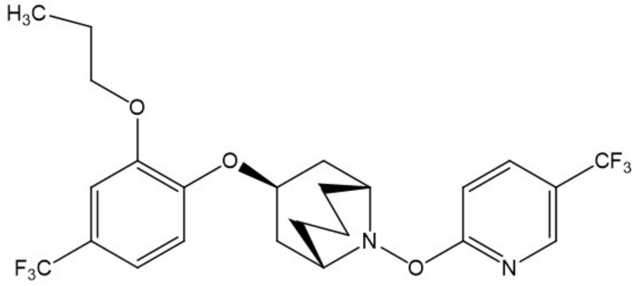
It is developed by Syngenta crop protection, registered in the year 2021. This is a novel isoxazoline insecticide and acaricide with good activity against Lepidopteran, Hemipteran, Coleopteran, Thysanopteran and Dipteran pest species. It is available in the name of Simodis® (Isocycloseram 9.2% w/w DC + Isocycloseram 10% w/v DC) in the market. It provides both contact and systemic action, ensuring thorough coverage and long-lasting pest control. Isocycloseram selectively targets the invertebrate Rdl GABA receptor at a site that is distinct to organochlorines.

1.7 Calcium-Activated Potassium Channel (KCa_2) Modulators

Insecticides targeting calcium-activated potassium channels (KCa_2) disrupt insect nervous systems by modulating these channels' activity. KCa_2 channels regulate neuronal excitability and neurotransmitter release in insects. Modulators interact with these channels upon ingestion or contact, either enhancing (activators) or inhibiting (inhibitors) their function. Activators increase potassium ion flow, leading to hyperexcitation and convulsions, while inhibitors decrease neuronal activity, resulting in paralysis and death. Selectivity for target insects is achieved by identifying specific KCa_2 channel subtypes prevalent in their nervous systems. These insecticides aim to minimize non-target effects, yet vigilance is required to manage potential resistance development. KCa2 modulator-based insecticides provide a targeted approach to pest control, offering potential environmental benefits compared to broad-spectrum alternatives. Allosterically activate nAChRs (at a site distinct from Group 5 - Site I), causing hyperexcitation of the nervous system.

1.7.1 Acynonapyr

This acaricide is discovered by Nippon Soda Co., Ltd., registered in March, 2019 in Japan. It contains N-pyridyloxy-azabicycle as a unique core structure. Acynonapyr (Fig. 1.6) at the concentration of 100–67 ppm is generally used and its application is currently expanding into fruit, tea, vegetables and flowering fields. It has a selective effect on spider mites of *Tetranychus* and *Panonychus*. Acynonapyr is found slightly toxic to fish. However, it is not toxic to mammals either *via* ingestion or in contact with the skin.



Acynonapyr

Fig. 1.6. Recent introduction of insecticide as Calcium-activated potassium channel (KCa_2) modulators.

1.8 Mitochondrial Complex III Electron Transport Inhibitors – Qi Site

Insecticides based on mitochondrial complex III electron transport inhibitors target the Qi site, a crucial component in the respiratory chain of insects. These inhibitors disrupt the transfer of electrons, preventing the conversion of ubiquinol to ubiquinone, a key step in oxidative phosphorylation. As a result, ATP production is hindered, leading to cellular energy depletion and eventual insect mortality. By selectively targeting the Qi site, these insecticides exhibit specificity towards insects while minimizing adverse effects on non-target organisms. Additionally, due to the fundamental role of mitochondrial respiration in insect physiology, resistance development is less likely compared to other insecticide classes. However, continuous monitoring for resistance is still necessary. In summary, insecticides targeting the Qi site provide an effective and selective method for pest control by disrupting insect energy metabolism and ultimately leading to insect death.

1.8.1 Flometoquin

It is a novel insecticide with a structurally unique phenoxy-quinoline. It was discovered in 2004 by the collaborative research of Nippon Kayaku and Meiji Seika Kaisha, Ltd. (currently, Mitsui Chemicals Crop & Life Solutions, Inc.) and registered in 2018. Through contact and feeding activity, the compound exhibits robust and fast insecticidal action against a range of thrips species at the nymphal and adult stages, which may reduce crop damage and financial loss caused by insect pest species. Furthermore, flometoquin (Fig. 1.7) has been shown to be safe for non-target arthropod testing, making it a good choice for managing insect pests in integrated pest management (IPM) programs. It is used in Cabbage; Cucumbers; Wheat; Fruit trees.

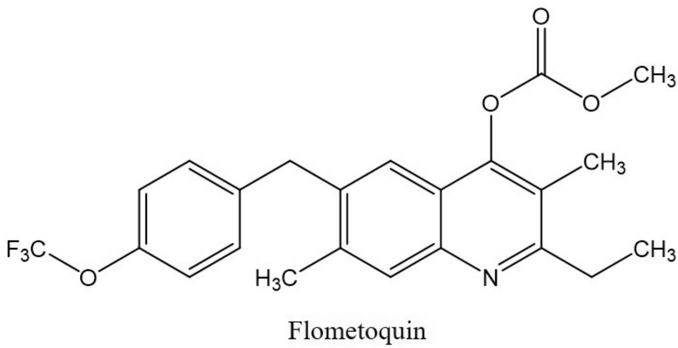


Fig. 1.7. Recent introduction of insecticide as mitochondrial complex III electron transport inhibitors – Qi site.

1.9 Constraints and Future Prospects

Insecticides have played a pivotal role in enhancing global agricultural production (Dalmolin et al. 2020). Certainly, many insecticides contributed enough in pest management. However, several incidences related to environmental and human toxicity, resistance, and resurgence of insect pests in several species on various crops has posed a serious threat (Ansari et al. 2014). Recently, consumers are highly cautious on the consumption of fresh produces treated with pesticides. Further, regulatory authorities have played important role on enforcement of strict rules and regulation on the handling of insecticides (Kaur et al. 2019).

There is an on-going need for the discovery and development of new insecticides due to the loss of existing products through the development of resistance, the desire for products with more favorable environmental and toxicological profiles, shifting pest spectrums, and changing agricultural practices. The number of research-based companies globally involved in the discovery of new insecticidal chemistries has been declining. The major challenge is the increasing costs involved in the discovery and development of new insecticides (Sparks et al. 2013). Despite increasing problems in the