Hormone Analogues and Chitin Synthesis Inhibitors

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Contents

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Omkar (ed.), *Molecular Approaches for Sustainable Insect Pest Management*,
https://doi.org/10.1007/978-981-16-3591-5_8

Abstract

The complexity of insect endocrine system can be well understood by studying different types of hormones, which include juvenile hormones, ecdysteroids and neuropeptide hormones. Juvenile hormone is basically a controlling hormone (control moults induced by ecdysone) for metamorphosis in insects. It also plays an important role in reproduction, diapauses of insects and caste determination. Ecdysteroids play a vital role in moulting, growth and development of insects. Depending upon the developmental stage of insect, they can act either as sole hormone or precursor for other ecdysteroid hormones. Neuropeptides commonly known as brain hormones are produced by neurosecretory cells of the central nervous system. The management of insect pests has become a greater challenge due to their ability to develop resistance to many insecticides. To conserve efficacy of insecticides for the control of insect pests, it is necessary to add diversity to the insecticidal pool by introduction of novel insecticides that are specific for biochemical sites or physiological processes in the target pest. Use of insect growth regulators (IGRs) is one of the approaches towards this kind of strategy. IGRs are biorational insecticides, which have novel modes of action causing disruption in the physiology and development of the target pest. IGRs are advantageous over conventional insecticides, as they are specific in action and have low toxicity towards nontarget organisms and mammals and lower rate of persistence in the environment. IGRs have been shown to cause numerous sublethal effects, viz. larval-pupal intermediate, adultoids, increase/decrease in fecundity, transovarial effects and developmental rate as well as changes in sex ratio, diapauses and morphology. Insect growth regulators are categorized into three types based on their mode of action, i.e. juvenile hormone analogues, ecdysone antagonists and chitin synthesis inhibitors. Presently, a number of commercial IGRs are available, but there is need for exploring more IGRs to expand our knowledge regarding their chemistry and effects on insect pests so that the use of these compounds could be expanded in integrated pest management programmes.

Keywords

Juvenile hormone · Ecdysteroids · Hormone antagonists · Chitin synthesis inhibitors · Integrated pest management

Learning Objectives

1. Categorization and functions of insect hormones, i.e. juvenile hormone, ecdysteroids and neurohormones.
2. Need of introduction of insect growth regulators (IGRs).
3. Different types of IGRs, i.e. juvenile hormone analogues, anti-juvenile hormones, ecdysone antagonists and chitin synthesis inhibitors.
4. Role of IGRs in integrated pest management.
5. Scope of anti-juvenoids in integrated pest management.

8.1 Introduction

Insect endocrine system is simpler, comprising of limited number of glands and tissues (Highnam 1967; Doucet et al. 2009). The secretions of the endocrine system, i.e. hormones, are chemical messengers or signals that play important role in coordination of various life processes, viz. development, physiological and behavioural processes, in insects (Highnam 1967; Doucet et al. 2009; Hoffmann and Lorenz 1998). Insect central nervous system (CNS) plays a crucial part in controlling hormonal secretions either directly or indirectly (Nijhout 1994; Reynolds 2013).

Integrated pest management was introduced in the twentieth century as a result of the negative impacts of broad-spectrum pesticides, such as organochlorines, organophosphates and carbamates (Kogan 1998; Doucet et al. 2009). These insecticides induced many ill effects on the environment, nontarget organisms and human health, via bioaccumulation, biomagnifications, persistence in the environment and toxicity. Along with these factors, the major issues were insecticide resistance and resurgence of new pest species. The main focus of IPM strategies was to lower the use of synthetic insecticides and application of safe alternatives. All this led to the introduction of chemicals to insecticidal pool, which were more specific in their mode of action (targeting particular physiological processes) and environment friendly (Doucet et al. 2009). The discovery of molecules that target insect endocrine system was part of this approach. The hormone analogues or antagonists are hormone mimics, which interfere in normal functioning of hormones and affect various physiological events in insect pests (Bowers 1971; Singh and Kumar 2011; Perner and Dhadialla 2012). This chapter will emphasize the role of these chemicals in integrated pest management.

8.2 Insect Hormones: Chemical Nature and Mode of Action

The principal hormones secreted by the endocrine system of insects are:

1. Juvenile hormones
2. Ecdysteroids
3. Neurohormones

8.2.1 Juvenile Hormone

This hormone is secreted by the corpus allatum and was first extracted by Williams in 1956 from the abdomens of adult male cecropia silk moth, *Hyalophora cecropia* (Highnam 1967; Roller et al. 1967; Minakuchi and Riddiford 2006). This acyclic sesquiterpene (Reynolds 2013; Goodman and Cusson 2012) is synthesized via the mevalonate pathway from farnesyl diphosphate or from one of its ethyl-branched

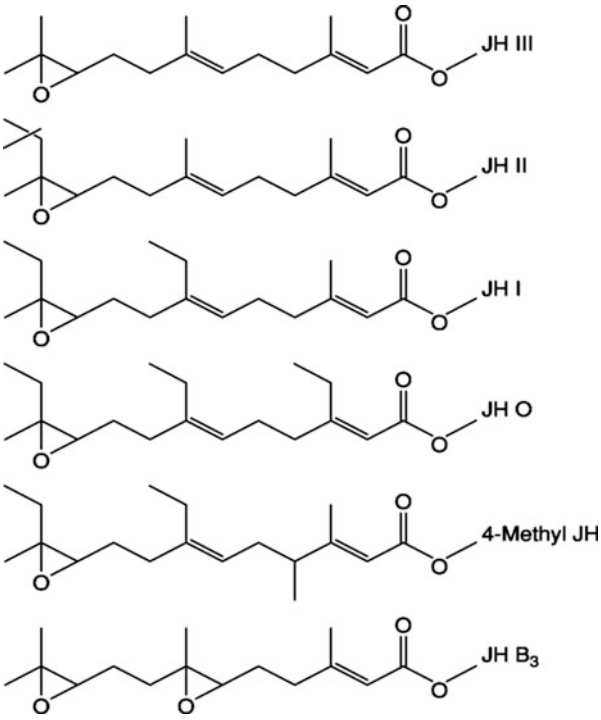


Fig. 8.1 Structure of juvenile hormones (Dhadialla et al. 2005)

homologues (Belles et al. 2005; Minakuchi and Riddiford 2006; Doucet et al. 2009; Singh and Kumar 2011; Goodman and Cusson 2012). Upon secretion juvenile hormone binds to juvenile binding proteins in the haemolymph of insect; this complex acts as a transportation source of juvenile hormones to target sites in insect's body (Mirth et al. 2005; Caldwell et al. 2005; Minakuchi and Riddiford 2006). There is no clarity about the molecular mechanism involved in mode of action of juvenile hormone (Minakuchi and Riddiford 2006; Reynolds 2013), as exact juvenile receptors are not identified.

There are different types of juvenile hormone identified in insects, i.e. JH 0, JH I, JH II and JH III. Most insects produce JH III, but Lepidoptera order is an exception, as it can synthesize JH 0, JH I, JH II and 4-methyl JH I (Fig. 8.1) (Schooley et al. 1984; Baker 1990). Bis-epoxy form of JH III is found in Diptera (Richard et al. 1989; Cusson et al. 1991; Minakuchi and Riddiford 2006; Goodman and Cusson 2012; Reynolds 2013). Juvenile hormones play an important role in regulation of development (growth and prevention of metamorphosis in larva), reproduction, stress response, behaviour, polyphenism and diapause (Goodman and Granger 2005a, b; Goodman and Cusson 2012; Noriega 2014).

8.2.2 Ecdysteroids

Ecdysteroids commonly termed as moulting hormones are polyhydroxylated derivatives of 7-dehydrocholestrol (Slama 2015; Gilbert et al. 1980; Milner et al. 1986) which are produced by the prothoracic glands in immature insects. In most adult insects, gonadal and other tissues may produce ecdysteroids upon degeneration of the prothoracic glands. The major ecdysteroid is 20E, but some insect species contain its homologues, i.e. makisterone A and makisterone C, respectively (Hoffmann and Lorenz 1998; Lafont et al. 2012). Ecdysone is generally considered to be a prohormone, being converted into the fat body or epidermis in most insects to the active hormone 20-hydroxyecdysone, by cytochrome P450 enzyme CYP314A. The steroids required for the synthesis of ecdysteroids are part of insect diet, as insects cannot produce steroids (Hoffmann and Lorenz 1998). Cholesterol is converted into ecdysteroid by a series of steps catalysed by P450 and several other enzymes. Phytophagous insects produce their own phytosterols as their diet lack cholesterol; as a result in some insects ecdysteroidogenesis begins with a different precursor, and the prothoracic glands secrete ecdysteroids other than ecdysone (Gilbert 1964; Highnam 1967; Hoffmann and Lorenz 1998; Reynolds 2013). The ecdysteroids form ecdysteroid receptor complex by binding with receptor molecule, which are site-specific DNA binding proteins (−100 kDa) in nucleus of the target cell. This complex further interacts with DNA to induce formation of new transcripts of RNA (Gade et al. 1997; Reynolds 2013; Uryu et al. 2015). Ecdysteroids act as moulting hormones, playing vital role in moulting of larvae and metamorphosis (Niwa and Niwa 2014; Uryu et al. 2015).

8.2.3 Neurohormones

Neurohormones also known as brain hormones of insects are peptides released by the neurosecretory cells of the central nervous system of insects (Highnam 1967; Hoffmann and Lorenz 1998). The diversity of these hormones is very large in insects (Reynolds 2013). There is a great variation in size of insect peptides according to the number of amino acid residues present in them, varying from lesser number of 5 residues (proctolin) to larger number of 62 residues found in eclosion hormone. The neuropeptide hormones can be either in the form of simple amino acid chains or modified post-translationally (Reynolds 2013). The neurohormones may act directly (adipokinetic hormone) on effector organs, or they may stimulate (prothoracicotropic hormone) other endocrine organs for the synthesis of hormones (Highnam 1967; Reynolds 2013). These hormones are also termed '**master regulators**' (Hoffmann and Lorenz 1998; Perić-Mataruga et al. 2006) as they regulate most of the physiological processes in insects, such as reproduction, development, behaviour, metabolism and homeostasis (Hoffmann and Lorenz 1998; Perić-Mataruga et al. 2006). Biogenic amines and adipokinetic hormones, neurohormones, control metabolism of carbohydrates and lipids. Ecdysiotropins or prothoracicotropic neurohormones (PTTH) stimulate the biosynthesis of ecdysteroid

in the prothoracic glands (Borovsky 2003; Gade and Goldsworthy 2003; Perić-Mataruga et al. 2006).

8.3 Concept of Insect Growth Regulators (IGRs) and Insect Growth Disruptors (IGDs)

Insect growth regulators (IGRs) were the result of quest to find insecticides with specific mode of action and which are safer for the environment and nontarget organisms with more selective modes of action (Staal 1975; Williams 1967; Altstein et al. 1993; Hoffmann and Lorenz 1998). Carroll Williams proposed the term '**third-generation pesticide**' in 1967 keeping in view the role of insect juvenile hormone (JH) as an insecticide (Dhadialla et al. 2005).

In the 1970s the term 'IGRs' was cited first time; Schneiderman (1972) used this term for hormone analogues or antagonists (juvenile hormones and ecdysones) that interrupt the regulation of growth and development in insects. Dhadialla et al. (2005, 2010) used the term insect growth disrupters instead of IGRs, as according to them these chemicals do not regulate endocrine processes but rather disrupt normal endocrine activities and, moreover, some chemicals such as chitin synthesis inhibitors (CSIs) are not involved directly in endocrine processes (Ioriatti et al. 2006; Slowik et al. 2001; Perner and Dhadialla 2012). Hence, these chemicals are a type of insecticides that disrupt the normal activity of the endocrine system, resulting in influences on growth, development, metamorphosis and reproduction of the target insect pests, and have slower mode of action as compared to the synthetic chemical insecticides (Staal 1982; Hoffmann and Lorenz 1998; Dhadialla et al. 2005). There are basically three types of IGRs that are commercially available:

1. Juvenile hormone analogues
2. Ecdysone agonists
3. Chitin synthesis inhibitors

8.3.1 Juvenile Hormone Analogues (JHA)

In the 1960s Schmialek (1961) discovered the first JHAs, farnesol and farnesal. Slama et al. (1974) found that both acyclic and cyclic compounds may act as JHAs. In 1972, methoprene became the first commercially available JHA. Most of the early JHAs were either synthesized (terpenoids) or procured naturally (juvabione) (Slama et al. 1974; Staal 1975; Henrick 2007; Ramaseshadri et al. 2012). The latter JHAs, i.e. fenoxycarb and pyriproxyfen, were more photostable and had broad-spectrum activity (Dorn et al. 1981; Masner et al. 1981; Grenier and Grenier 1993; Hatakoshi et al. 1986; Dhadialla et al. 1998; Perner and Dhadialla 2012).

The general assumption about JHAs is that they mimic the action of naturally occurring JH and affect all functions. However, only few of such functions are

explored for the management of insect pests (Retnakaran et al. 1985). The hormonal effects that are exploited for the control of insect pests are:

1. Interference of normal metamorphosis of last instar larva, resulting in larva-pupal intermediates (Retnakaran 1973a, b; Retnakaran et al. 1985; Dhadialla et al. 2005).
2. JHAs block embryonic development at blastokinesis stage and induce ovicidal effects (Riddiford and Williams 1967; Masner et al. 1968; Retnakaran 1970; Riddiford 1971; Dhadialla et al. 2005).
3. Induction of sterility in adults (Langley et al. 1990; Dhadialla et al. 2005).
4. Termination of reproductive diapauses (De Wilde et al. 1971; Retnakaran 1974; Dhadialla et al. 2005).

8.3.1.1 Commercially Available Juvenile Analogues and Their Role

Methoprene

Methoprene is terpenoid, which lacks the epoxide function present in JH (Ashok et al. 1998; Wilson and Ashok 1998; Hoffmann and Lorenz 1998; Dhadialla et al. 2005). Methoprene is most studied and relatively nontoxic to most nontarget organisms. Methoprene half-life is 10 days in soil and is rapidly broken down and excreted. This JHA also shows larvicidal property for controlling many insects of the order Coleoptera, Diptera, Homoptera and Siphonaptera (Harding 1979; Hoffmann and Lorenz 1998; Dhadialla et al. 2005) (Fig. 8.2).

Kinoprene

This JHA has very low or no toxicity. It is non-persistent, easily decomposes on sun exposure and is nontoxic to nontargets and beneficial insects. It induces ovicidal, morphological and sterilant effects in insect pests and is effective in the control of whiteflies, scales, aphids, mealybugs and fungal gnats (Harding 1979; Dhadialla et al. 2005).

Fenoxycarb

Fenoxycarb is phenoxy JHA having carbamate moiety, which is very effective in the control of cockroaches, sucking insects, fleas, fire ants, mosquitoes and scale insects (Grenier and Grenier 1993). Unlike other JHAs, it is slightly toxic to nontargets (aquatic crustaceans and beneficial insects (neuropterans)) (Liu and Chen 2001; Dhadialla et al. 2005) (Fig. 8.2).

Pyriproxyfen

This JHA, also a phenoxy analogue, is one of the most potent JHAs. It causes morphogenetic and sterility in target insects. It has been used for controlling aphids, scales, fire ants, whiteflies and pear psylla. It is, however, mildly toxic to some aquatic organisms but nontoxic to beneficial insects, like bees (Langley et al. 1990; Dhadialla et al. 2005) (Fig. 8.2).

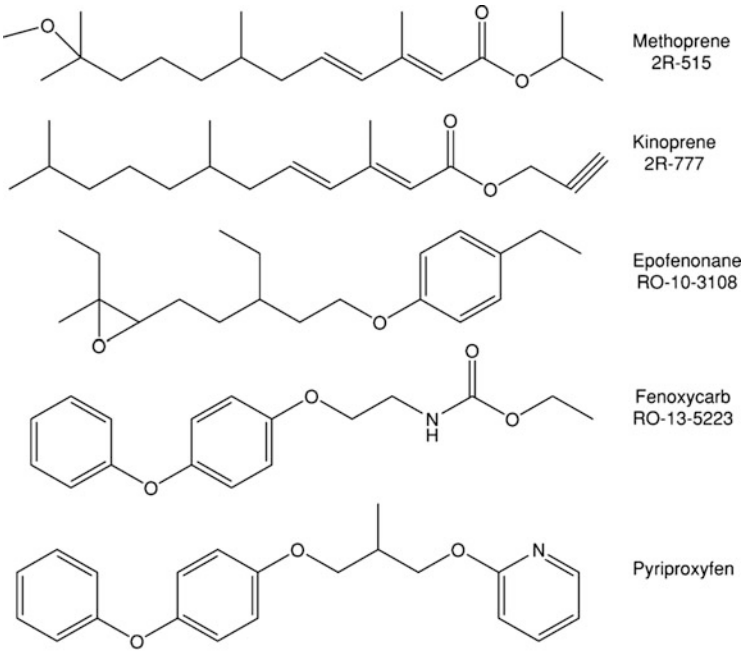


Fig. 8.2 Structures of juvenile hormone analogues (Dhadialla et al. 2005)

8.3.2 Ecdysone Antagonists

Hsu (1991) discovered the first bisacylhydrazine ecdysone agonist, which was further altered to more potent and unsubstituted analogue RH-5849. This analogue possessed broad-spectrum activity and was effective against insect pests of Lepidoptera, Coleoptera and Diptera orders (Aller and Ramsay 1988; Wing et al. 1988; Wing and Aller 1990; Dhadialla et al. 2005). Further research resulted in discovery of cost-effective, highly selective and more potent bisacylhydrazines, such as tebufenozide, methoxyfenozide and halofenozide (Dhadialla et al. 1998, 2005). Tebufenozide and methoxyfenozide are selectively toxic to larvae of lepidopteran insect pests (Hsu 1991). However, methoxyfenozide is more efficacious as compared to tebufenozide and is toxic to a wider range of lepidopteran and other insect pests (Ishaaya et al. 1995; Le et al. 1996; Trisyono and Chippendale 1997; Dhadialla et al. 2005). Halofenozide has a broad spectrum and is effective for the control of cutworms, scarab beetle larvae and webworms (RohMid LLC 1996). Chromafenozide is another bisacylhydrazine used for the control of lepidopteran larvae (Yanagi et al. 2000; Ichinose et al. 2000; Toya et al. 2002; Dhadialla et al. 2005).

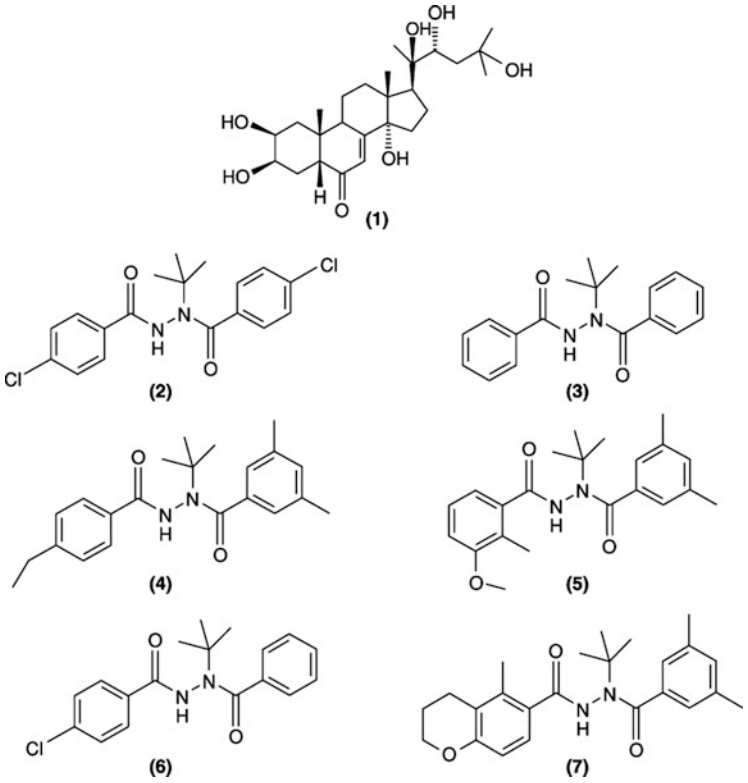


Fig. 8.3 Chemical structures of 20-hydroxyecdysone (1), symmetrically substituted dichlorodibenzoylhydrazine (2), RH-5849 (3), tebufenozide (4), methoxyfenozide (5), halofenozide (6), chromafenozide (7) (Dhadialla et al. 2005)

8.3.2.1 Commercially Available Ecdysone Antagonists and Their Role

Chromafenozide

It is a nonsteroidal ecdysone agonist developed jointly by Nippon Kayaku Co., Ltd. (Saitama, Japan), and Sankyo Co., Ltd. (Ibaraki, Japan). It is registered for the management of lepidopteran pests on vegetables, fruits, vines, tea, rice, arboriculture, ornamentals and other crops in Japan (Yanagi et al. 2000; Ichinose et al. 2000; Toya et al. 2002). Chromafenozide is safe for mammals, birds, aquatic animals and other nontarget and beneficial insects (Dhadialla et al. 2005) (Fig. 8.3).

Halofenozide

It is a systemic compound having broad-spectrum activity. It is effective for the control of beetle grubs (Japanese beetle, oriental beetle, June beetle, northern and southern masked chafer, green June beetle, black turfgrass ataenius beetle, annual bluegrass weevil larvae, *Aphodius* beetles, European chafer and bill bugs) and

lepidopteran larval pests (cutworms, sod webworms, armyworms and fall armyworms) (Cowles and Villani 1996; Cowles et al. 1999; Dhadialla et al. 2005) (Fig. 8.3).

Tebufenozide and Methoxyfenozide

Tebufenozide is used for the control of lepidopteran larvae and insect pests from families Noctuidae, Pyralidae, Tortricidae and Pieridae (Le et al. 1996; Dhadialla et al. 1998; Carlson et al. 2001). Both tebufenozide and methoxyfenozide act primarily by ingestion mode but also possess contact and ovicidal activity (Trisyono and Chippendale 1997; Sun and Barrett 1999; Sun et al. 2000; Dhadialla et al. 2005) (Fig. 8.3).

8.3.3 Chitin Synthesis Inhibitors

Chitin is a β-1,4-linked amino polysaccharide homopolymer of *N*-acetylglucosamine (GlcNAc) and cross-linked to proteins via biphenyl linkages to form chitin microfibers–protein complex which acts as a protective matrix (Lotmar and Picken 1950; Rudall and Kenchington 1973; Dhadialla et al. 2005; Doucet and Retnakaran 2012). Chitin is a major component of the outermost layer of insect integument called cuticle. Insect's peritrophic matrix is also constituted of chitin, which acts as a permeability barrier between the food bolus and epithelium of the midgut and protects the gut from injury, toxins and pathogens. The chitin synthesis and degradation in insect body is consistent in a highly controlled manner to allow both regeneration and ecdysis of the peritrophic matrix (Locke 1991; Moussian 2010; Vincent and Wegst 2004; Doucet and Retnakaran 2012).

Chitin biosynthesis is initiated with the disaccharide trehalose, finally resulting in the *N*-acetylglucosamine subunit polymerization by enzyme chitin synthase leading to the production of chitin microfibrils. Enzymes, such chitinases, deacetylases and hexosaminidases, help in the degradation and recycling of old chitin exoskeleton. Chitin synthesis is a key target process used for the development of biorational insecticides, such as benzoylphenyl ureas, which act as chitin synthesis inhibitors (Doucet and Retnakaran 2012).

In the 1970s the first chitin synthesis inhibitor, diflubenzuron, belonging to the benzoylphenyl urea class of chemistry, was discovered by Philips-Duphar Company (Miyamoto et al. 1993; Tunaz and Uygun 2004; Subramanian and Shankarganesh 2016). The discovery of diflubenzuron resulted in the development of a number of other derivatives of BPU, such as triflumuron, chlorfluazuron, teflubenzuron, hexaflumuron, flufenoxuron, novaluron and lufenuron (Hamman and Sirrenberg 1980; Haga et al. 1982; Becher et al. 1983; Sbragia et al. 1983; Anderson et al. 1986; Ishaaya et al. 1996; Subramanian and Shankarganesh 2016). The non-BPU compounds, which are developed recently, include etoxazole, buprofezin, cyromazine and dicyclanil (Ishida et al. 1994; Dhadialla et al. 2005; Subramanian and Shankarganesh 2016).

Chitin synthesis inhibitor compounds act on insects through inhibition of chitin formation, abnormal endocuticular deposition and abortive moulting (Ishaaya and Casida 1980; Dhadialla et al. 2005; Merzendorfer 2013).

These are divided into two categories on the basis of their chemistry, i.e.:

1. Benzoylphenyl ureas (BPUs)
2. Non-benzoylphenyl ureas (non-BPUs)

8.3.3.1 Benzoylphenyl Ureas

Benzoylphenyl urea compounds have a central urea moiety; the phenyl end generally is the site of most complex substitutions, while the benzoyl part remains relatively simple. It is assumed that the benzoyl part of BPUs gets attached to the unidentified receptor, which results in chitin synthesis inhibition (Nakagawa et al. 1991; Dhadialla et al. 2005; Doucet and Retnakaran 2012; Subramanian and Shankarganesh 2016). Benzoylphenyl urea compounds generally have a common mode of action and block a postcatalytic step in chitin biosynthesis process (Nauen and Smagghe 2006; Van Leeuwen et al. 2012), e.g. diflubenzuron, bistrifluron, chlorbenzuron, novaluron, lufenuron, hexaflumuron etc. (Doucet and Retnakaran 2012) (Fig. 8.4).

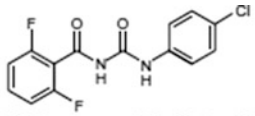
Commercially Available Benzoylphenyl Ureas and Their Role in Pest Management

Chlorfluazuron

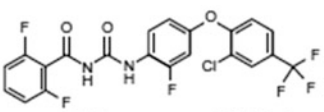
Chlorfluazuron is a broad-spectrum BPU compound, being actively used against most lepidopteran, coleopteran, hymenopteran and dipteran insect pests along with thrips and whiteflies. It is an environmentally safe compound and has ingestion as route of action. It also has a very low toxic effect on adult egg of parasitoids and is safe for beneficial insects as compared to other synthetic insecticides (Wang et al. 2012; Rabea et al. 2010). Chlorfluazuron is also helpful in controlling the Formosan subterranean termite, *Coptotermes formosanus*, and the eastern subterranean termite, *Reticulitermes flavipes* (Dhadialla et al. 2005; Osbrink et al. 2011; Doucet and Retnakaran 2012).

Diflubenzuron

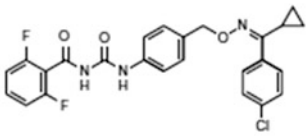
Diflubenzuron is nonsystemic and is the most studied and extensively used BPU worldwide (Doucet and Retnakaran 2012). This highly water-insoluble compound has stomach and contact toxicity. It has to be ingested to be effective. It does not affect sap-sucking insects, as it is nonsystemic to plants. It is not effective for all lepidopteran larvae due to variation in detoxification processes among different species. The developmental stage of larvae also influences the effectiveness of the compound, as in the case of spruce budworm, *Choristoneura fumiferana*, in which the larvae of the fifth and sixth instars were more susceptible to diflubenzuron as compared to the earlier stages (Granett and Retnakaran 1977). The fruit tortrix moths *Adoxophyes orana* and *Pandemis heparana* are relatively insensitive to



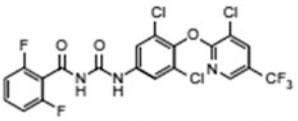
Diflubenzuron (Dimilin)— Philips-Duphar BV 1972



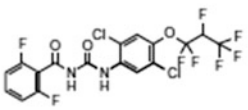
Flufenoxuron — Shell International Co.Ltd. 1987



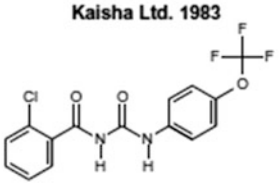
Fluxyloxuron (PH 60-23)— Philips-Duphar BV 1988



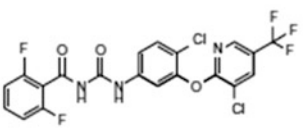
Chlorfluazuron— Ishihara Sangyo Kaisha Ltd. 1983



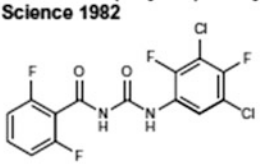
Lufenuron — Novartis A.G. 1977



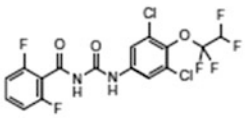
Triflumuron (Alsystin) — Bayer Crop Science 1982



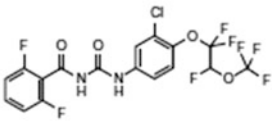
Fluazuron — Novartis A.G. 1990



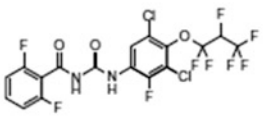
Teflubenzuron — Celamerck GmBH. 1982



Hexaflumuron — Dow Elanco Ltd. 1984



Novaluron — Makhteshim Agan Industries 1990



Noviflumuron — Dow Agro Sciences LLC. 2001

Fig. 8.4 Chemical structures of commercialized benzoylphenyl ureas (Doucet and Retnakaran 2012)

diflubenzuron, while the forest tent caterpillar, *Malacosoma disstria*, and the gypsy moth, *Lymantria dispar*, are sensitive (Eck 1981; Retnakaran et al. 1985). It has been used to control cockroaches, locusts, grasshoppers, larvae of sciarid flies, phorid flies, mosquitoes and insect pests of cotton, horticultural crops and soybean (Weiland et al. 2002). Diflubenzuron is less effective for the control of Colorado

potato beetle, *Leptinotarsa decemlineata*, than other BPU, such as lufenuron (Karimzadeh et al. 2007). Diflubenzuron is nontoxic to beneficial insects (bees), mammals and birds; however, crustaceans are sensitive to it (Dhadialla et al. 2005; Gartenstein et al. 2006; Doucet and Retnakaran 2012).

Flucycloxuron

This BPU compound has topical contact activity and is mainly used as an acaricide (Doucet and Retnakaran 2012). Flucycloxuron is used for the control of both tetranychid and eriophyid mites. It penetrates the leaf cuticle and is shown to have ovicidal, transovarial-ovicidal and ovo-larvicidal effects in target organisms. According to Grosscurt (1993), it was effective on the two-spotted spider mite, *Tetranychus urticae*, and the European red mite, *Panonychus ulmi*, on apple leaves. It is similar to diflubenzuron in terms of toxicity but might be more toxic to aquatic organisms, such as rainbow trout, *Oncorhynchus mykiss*, and water flea, *Daphnia* (Darvas and Polgar 1998; Dhadialla et al. 2005; Doucet and Retnakaran 2012).

Fluazuron

Fluazuron has been shown to be effective against ticks (*Rhipicephalus sanguineus*) and mites (*Sarcoptes scabiei*) (De Oliveira et al. 2012; Pasay et al. 2012). The population of flea was successfully lowered in squirrels and mice by application of fluazuron (Dhadialla et al. 2005; Davis et al. 2008; Doucet and Retnakaran 2012).

Flufenoxuron

Flufenoxuron is used against the larvae of lepidopteran insects on vegetables, fruits, cotton and grain crops (Doucet and Retnakaran 2012). It is second best control measure for *Spodoptera littoralis* after lufenuron (El-Sheikh and Aamir 2011). It is also very effective as a control of mushroom sciarid fly, *Lycoriella ingenua*, as compared to novaluron, diflubenzuron and teflubenzuron (Dhadialla et al. 2005; Doucet and Retnakaran 2012; Erler et al. 2011).

Hexaflumuron

Hexaflumuron has been used against the larvae of Lepidoptera, Coleoptera and Diptera (Doucet and Retnakaran 2012). It is also effective against termite, *Reticulitermes flavipes* and *Coptotermes formosanus*, following incorporating it in bait (Dhadialla et al. 2005; Messenger et al. 2005; Ripa et al. 2007; Doucet and Retnakaran 2012).

Lufenuron

This BPU is extensively used in controlling fly pests (*Lycoriella ingénue*) of common mushroom, *Agaricus bisporus* (Erler et al. 2011; Doucet and Retnakaran 2012). Lufenuron has been also effective against termites, *Reticulitermes hesperus* (Haverty et al. 2010). Lufenuron causes transovarial-ovicidal and larvicidal effects; due to this property, it has been used against many lepidopteran pests. It has low toxicity against many parasitoids and has adequate persistence making it effective on many pests. Tortricid, the light brown apple moth, *Epiphyas postvittana*, can also be

controlled by lufenuron (Whiting et al. 2000; Dhadialla et al. 2005; Doucet and Retnakaran 2012).

Triflumuron

Triflumuron is a broad-spectrum BPU, which is effective against cabbage moth, apple leaf miner, boll worm, codling moth, psyllids, cotton leafworm, tortrix moth, summer fruit moth and many other insect pests (Doucet and Retnakaran 2012). Triflumuron is the most effective among BPU compounds for the management of mushroom sciarid, *Lycoriella ingenua* (Erler et al. 2011). It is used successfully for the control of mealworm, *Alphitobius diaperinus*, when used in combination with pyrethroid insecticides (Salin et al. 2003). It induces ovicidal and larvicidal activities making it an ideal candidate for the control of flies also (Smith and Wall 1998; Broadbent and Pree 1984; Hejazi and Granett 1986; Asher and Nemny 1984; Dhadialla et al. 2005; Vazirianzadeh et al. 2007; Doucet and Retnakaran 2012).

Teflubenzuron

Teflubenzuron hindered the egg hatching in females of migratory locust, *Locusta migratoria* (Acheuk et al. 2012; Doucet and Retnakaran 2012). It also reduces sea lice (ectoparasite), *Lepeophtheirus salmonis*, population in Atlantic salmon fish farms (Dhadialla et al. 2005; Campbell et al. 2006; Doucet and Retnakaran 2012).

Noviflumuron

This BPU is effective against cockroaches and termites (*C. formosanus*) (Ameen et al. 2005; Dhadialla et al. 2005; Husseneder et al. 2007; Doucet and Retnakaran 2012).

Novaluron

It is an effective agent in the control of several lepidopteran, dipteran, coleopteran and homopteran pests (Doucet and Retnakaran 2012). It has low acute toxicity against mammals and poses low risk to nontarget organisms and the environment. It is an ideal candidate for IPM and integrated resistance management (IRM) programmes (Cutler and Scott-Dupree 2007). Novaluron is used for the management of many important pests, such as leaf miners, whiteflies and beet armyworm (Ishaaya and Horowitz 1998; Ishaaya et al. 1996). In Brazil, it is successfully used to reduce the population of mosquito, *Aedes aegypti* (Dhadialla et al. 2005; Doucet and Retnakaran 2012; Farnesi et al. 2012).

8.3.3.2 Non-benzoylphenyl Ureas

The non-benzoylphenyl urea class of compounds, viz. buprofezin, etoxazole, cyromazine and dicyclanil, has been used widely for the control of insect pets in agricultural and public health systems (Subramanian and Shankarganesh 2016). Buprofezin belonging to the group of thiadiazines acts on insects by inhibition of cuticle deposition, chitin biosynthesis, lamellate cuticle formation and inhibition of cholinesterase activity (Cottage and Gunning 2006; Subramanian and Shankarganesh 2016). Cyromazine and dicyclanil interfere with cuticle formation

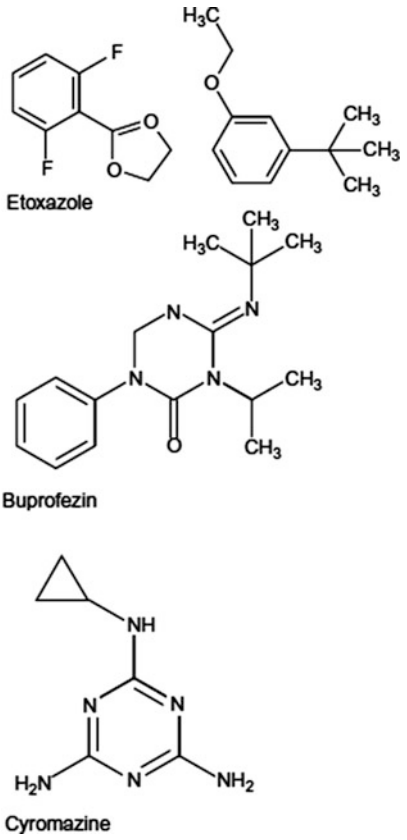


Fig. 8.5 Chemical structures of commercialized non-benzoylphenyl ureas (Doucet and Retnakaran 2012)

and do not inhibit chitin synthesis, and so are considered as moult inhibitors. Cyromazine, an aminotriazine and a cyclopropyl derivative of melamine, is commercially available under the trademarks Neoprex, Trigard and Vetrazin and provides a good control measure for stable flies in winter hay (Taylor et al. 2012). Dicyclanil (CliK) is efficacious against sheep and lamb blowflies (Dhadialla et al. 2005; Cohen 2010; Doucet and Retnakaran 2012; Subramanian and Shankarganesh 2016) (Fig. 8.5).

Commercially Available Non-benzoylphenyl Ureas and Their Role in Pest Management

Buprofezin

Buprofezin, 2-tert-butylimino-5-phenyl-3-propan-2-yl-1,3,5-thiadiazinan-4-one, developed by Hoechst acts specifically on immature developmental stages of some homopteran (scale insects, mealybugs and whiteflies) pests by inhibiting *N*-acetyl-[D-H3] glucosamine incorporation into chitin and thus disrupting the cuticle formation, which leads in nymphal mortality during ecdysis (Ishaaya and Horowitz 1998;

Kanno et al. 1981; Nasr et al. 2010; Doucet and Retnakaran 2012). This compound also acts on cholinesterase, suppresses oviposition in adults and reduces viability of eggs. It has been used extensively against the whitefly *Bemisia tabaci* (Cottage and Gunning 2006). It is mildly toxic to mammals but generally nontoxic to birds (Palli and Retnakaran 1998; Dhadialla et al. 2005; Doucet and Retnakaran 2012).

Etoxazole

Yashima Chemical Industry Co., Japan, developed this non-BPU compound in 1994. It acts as acaricide for the control of tetranychid spider mites (*Panonychus* and *Tetranychus* species) (Yagi et al. 2000; Suzuki et al. 2001, 2002; Tisdell et al. 2004; Hirose et al. 2010; Doucet and Retnakaran 2012; Li et al. 2014). It inhibits moulting during the development of insects and mites (Lee et al. 2004; Asahara et al. 2008; Sun et al. 2008). It is also effective against leafhoppers, aphids, fall armyworm and diamond back moth (Nauen and Smagghe 2006). In case of spider mites, it affects only the eggs, larvae and nymphs but not adults. Etoxazole degradation in the soil is slow and also undergoes partial photolysis (Dhadialla et al. 2005; Doucet and Retnakaran 2012).

Cyromazine

Cyromazine (CGA 72662, *N*-cyclopropyl-1,3,5-triazine-2,4,6-triamine) discovered by Ciba-Geigy, Ltd., in the 1970s is an aminotriazine and a cyclopropyl derivative of melamine (Shen and Plapp 1990; Vazirianzadeh et al. 2007; Doucet and Retnakaran 2012). It has both insecticidal and acaricidal activity and has contact activity that inhibits moulting and pupation in target pests (Patakioutas et al. 2007). It has been successfully used for the control of insect pests of vegetables, mushrooms and ornamentals. It is also helpful in the management of stable fly maggots in winter hay (Dhadialla et al. 2005; Doucet and Retnakaran 2012; Taylor et al. 2012).

8.4 Anti-juvenile Hormones

The anti-JH agents are compounds that have property of inhibiting the biosynthesis of JH in insects, eventually leading to halting of biological processes under the control of JH (Staal 1986; Darvas et al. 1990; Goodman and Granger 2005a, b; Ghoneim and Bakr 2018). The sublethal affects include inhibition of growth and development, deranged morphogenesis, precocious metamorphosis, lower rates of adult emergence and reduced survival of adults (Ghoneim and Bakr 2018). These compounds also possess anti-gonadotropic activity, affecting oocyte maturation, oviposition and reproductive capacity in insects (Ghoneim and Bakr 2018). Bowers et al. (1976) were first to discover the insect anti-JHs, i.e. precocenes I and II (Minakuchi and Riddiford 2006; Ghoneim and Bakr 2018). Further research leads to the synthesis of synthetic precocenoids and other anti-JH compounds including fluoromevalonate, ethyl-4-[2-(tert-butylcarbonyloxy)butoxy]benzoate (ETB), compactin, EMD, dichloroallyl hexanoate, KK-42, KK-110, brevioxime, terpenoid and 1,5-disubstituted imidazoles (Quistad et al. 1981; Staal et al. 1981; Farag and

Varjas 1983; Hiruma et al. 1983; Staal 1986; Kuwano et al. 1988; Darvas et al. 1990; Castillo et al. 1998). Most of these compounds induce precocious metamorphosis, but black pigmentation (piperonyl butoxide and thiolcarbamates) was also reported in few cases (Kramer et al. 1983; Ghoneim and Bakr 2018).

8.4.1 Precocenes

Precocenes, plant-derived chromenes (Ghoneim and Bakr 2018), were isolated by Bowers et al. (1976) from *Ageratum houstonianum* and termed them as precocenes I (7-methoxy-2,2-dimethylchromene) and precocenes II (6,7-dimethoxy-2,2-dimethylchromene) (Bowers 1976, 1992; Proksch et al. 1983; Isman et al. 1986; Minakuchi and Riddiford 2006; Ghoneim and Bakr 2018). These compounds were known to induce cytotoxicity in corpora allata in insects, resulting in the prohibition of juvenile hormone biosynthesis (Pratt et al. 1980; Schrankel et al. 1982; Minakuchi and Riddiford 2006; Ghoneim and Bakr 2018). Holometabolous insect larvae are less susceptible to precocenes action, which could be due to sequestration and detoxification (Burt et al. 1979; Haunerland and Bowers 1985; Minakuchi and Riddiford 2006). However, some holometabolous insects, i.e. lawn armyworm, *Spodoptera mauritia*, and the Egyptian cotton leafworm, *Spodoptera littoralis*, are exceptions, as they are found to be susceptible (Mathai and Nair 1984; Khafagi and Hegazi 2001; Ghoneim and Bakr 2018). These compounds also affect non-social insects by inducing precocious metamorphosis during the pre-adult stages (Khan and Kumar 2000, 2005; Gaur and Kumar 2009; Ghoneim and Bakr 2018). They also halt vitellogenic development of the oocytes, leading to sterility, thus affecting the reproduction in many insect orders (Staal 1986; Kumar and Khan 2004; Amiri et al. 2010; Ghoneim and Bakr 2018). Precocenes induces early diapauses in insects and also influences insect behaviour, i.e. mating, flight, maternal defense and sexual behaviour (Bowers 1983; Walker 1978; Rankin 1980; Kight 1998; Pathak and Bhandari 2002; Ringo et al. 2005; Ghoneim and Bakr 2018). They also have property of inhibiting sex pheromone production and possess antifeedant and repellent activities (Bowers 1983; Khafagi 2004; Lu et al. 2014; Ghoneim and Bakr 2018). Precocenes are mainly used for experimental purposes only for studying activity of juvenile hormone on development and reproduction in insects (Minakuchi and Riddiford 2006).

8.4.2 Fluoromevalonate (FMeV)

FMev (tetrahydro-4-fluoromethyl-4-hydroxy-2*H*-pyran-2-one) is an anti-JH compound, highly effective and selective against various lepidopteran species, i.e. *Spodoptera exigua*, *Manduca sexta*, *Galleria mellonella*, *Samia cynthia*, *Hyphantria cunea*, *Phryganidia californica* and *Heliothis virescens* (Quistad et al. 1981; Edwards et al. 1983; Ghoneim and Bakr 2018). Non-lepidopteran species are not susceptible to FMeV (Menn 1985). The definite mode of action of this

compound in insects is not yet clear. It is assumed that FMev disrupts metabolism of mevalonate by inhibiting the initial steps in juvenile hormone biosynthetic pathway (Quistad et al. 1981; Baker et al. 1986). Precocious pupation is characteristic response of FMev treatment (Kramer and Staal 1981; Farag and Varjas 1983; Ghoneim and Bakr 2018).

8.4.3 Terpenoid Imidazoles

The major active anti-juvenile hormone compounds of this group were KK-22 and KK-42 (Kuwano and Eto 1983; Akai et al. 1984; Ghoneim and Bakr 2018). KK-22 induces precocious metamorphosis (Asano et al. 1984). KK-42 inhibits juvenile hormone and ecdysone synthesis and affects the growth and development of insect species (Kuwano et al. 1992; Kadano-Okuda et al. 1994; Kadono-Okuda et al. 1987; Minakuchi and Riddiford 2006; Ghoneim and Bakr 2018).

8.4.4 Derivative of Fungi and Bacteria Anti-juvenile Hormone Compounds

These includes brevioxime, compactin, fluvastatin (fungi-derived) and cycloheximide (bacteria-derived). Brevioxime is derivative of entomopathogenic fungus, *Penicillium brevicompactum*, and possesses strong anti-JH activity against *Oncopeltus fasciatus* (Castillo et al. 1999; Ghoneim and Bakr 2018). Compactin strongly inhibits JH biosynthesis in *Manduca sexta*, *Mamestra brassicae* and *Periplaneta americana* (Monger et al. 1982; Hiruma et al. 1983; Edwards and Price 1983; Ghoneim and Bakr 2018). Fluvastatin treatment results in the inhibition of JH-regulated metamorphosis in locust, *Locusta migratoria* (Debernard et al. 1994), and halts JH acid biosynthesis in the black cutworm, *Agrotis ipsilon* (Duportets et al. 1996; Ghoneim and Bakr 2018). Cycloheximide isolated from the bacterium *Streptomyces griseus* is a RNA (*L. migratoria*) and protein synthesis inhibitor (*Spodoptera frugiperda*) (Siegel and Sisler 1963; Baliga et al. 1969; Kelly and Lescott 1976; Phillips and Loughton 1979).

8.4.5 Benzoate and Methyl Dodecanoate Compounds

The benzoate compound ETB (ethyl-4-[2-(tert-butylcarbonyloxy)butoxy]benzoate) developed in 1975 (Minakuchi and Riddiford 2006; Ghoneim and Bakr 2018) reduces the level of juvenile hormone (anti-juvenile activity) in *M. sexta* and *B. mori* resulting in precocious metamorphosis (Kiguchi et al. 1984; Minakuchi and Riddiford 2006; Ghoneim and Bakr 2018). EMD (ethyl-[*E*]-3-methyl-2-dodecanoate) exhibits anti-JH effects on the tobacco budworm *Heliothis virescens* and *M. sexta* (Staal 1982). In a study conducted on *B. mori* larvae, no precocious metamorphosis was induced by EMD in the third and fourth instars (Kuwano et al.

1988). Balamani and Nair (1989) found the formation of larval-pupal intermediates in *Spodoptera mauritia* upon treatment with EMD (Ghoneim and Bakr 2018).

8.4.6 Bisthiolcarbamate and Sulphoxides

Bisthiolcarbamate treatment of the third instar larvae of *M. sexta* resulted in suppression of JH titre. Precocious pupation was not observed, but black pigmentation was reported with this compound. Rapid degradation was the main reason for the weak activity of bisthiolcarbamate (Kramer et al. 1983; Ghoneim and Bakr 2018). The anti-JH activity of the compound polyacetylene sulphoxide was first revealed by Bowers and Aregullin (1987). This compound induced sterility in adults of *O. fasciatus*. In the 1980s a number of fluorinated vinyl sulphoxides were developed, which were effective against Lepidoptera order (Carney and Brown 1989; Ghoneim and Bakr 2018).

Although anti-JH compounds possess advantage of being selectively toxic, halting major physiological processes in target insects, still the commercialization of these compounds has not been yet achieved as the majority of the studies on these compounds have been conducted in laboratory conditions, while the field investigations remained untouched (Minakuchi and Riddiford 2006; Ghoneim and Bakr 2018).

8.5 Neuropeptide Hormones as Potential Candidates for Pest Management: A Future

Neuropeptide hormones act as key regulators of vital physiological processes in insects, such as reproduction, growth, development, metabolism and homeostasis. The quality of these hormones could be explored for the development of their analogues or agonists, making them potential tool for insect pest control (Fonagy 2006; Altstein 2001). Analogues could possibly interfere with synthesis and secretion of neuropeptides and affect receptors (Gade and Goldsworthy 2003). Although use of neuropeptide antagonists could be very effective in the management strategy, it is not implemented till date due to few but major limitations:

1. Linear structure of peptides makes them nonselective, hinders penetration through tissues of target pests and increases susceptibility to proteolytic degradation (Altstein 2001).
2. Lack of knowledge about the three-dimensional structure of receptor-agonist complex and mechanism of activation of this receptor (Altstein 2001).

According to Altstein (2001), the backbone cyclic neuropeptide-based antagonist (BBC-NBA) approach could be effectively used to overcome limitations for the generation of neuropeptide antagonists. This technique is applied to the insect, pyrokinin (PK)/pheromone biosynthesis activating neuropeptide (PBAN), leading

to production of linear lead antagonist and metabolically stable backbone cyclic antagonists, which lack agonistic activity and inhibit activities in insects mediated by PBAN. This approach is adeptly used in inhibition of sex pheromone biosynthesis in adult female of *Helicoverpa peltigera* and cuticular melanin formation in larvae of *Spodoptera littoralis* (Altstein et al. 1996, 1999; Altstein 2001).

8.6 Conclusions

JHAs and CSIs among IGRs can become a viable component of IPM programme if used judiciously, and many commercial formulations of these are available. These are less toxic to natural enemies of insects. Low mammalian toxicity, biodegradability and specific nature of these compounds make them ecofriendly. The novel mode of action of IGRs reduces the risk of cross-resistance. There is an urgent need to have better field stable formulations of IGRs mainly photostable formulations, which should also be cost-effective for large-scale use.

Points to Remember

- The complexity of insect endocrine system can be well understood by studying different types of hormones, which include juvenile hormones, ecdysteroids and neuropeptide hormones.
- Juvenile hormone is basically a controlling hormone (control moults induced by ecdysone) for metamorphosis in insects. It also plays an important role in reproduction, diapauses of insects and caste determination.
- Ecdysteroids play vital role in moulting, growth and development of insects. Depending upon stage of insect, they act as either sole hormone or precursor for other ecdysteroid hormones.
- Neuropeptides, commonly known as brain hormones, are produced by neurosecretory cells of the central nervous system. The management of insect pests has become a greater challenge due to their ability to develop resistance to many insecticides.
- To conserve efficacy of insecticides for the control of insect pests, it is necessary to add diversity to the insecticidal pool by introduction of novel insecticides that are specific for biochemical sites or physiological processes in the target pest.
- IGRs are biorational insecticides, which have novel modes of action, causing disruption in the physiology and development of the target pests.
- IGRs are advantageous over conventional insecticides, as they are specific in action and have low toxicity to nontarget organisms and mammals and lower rate of persistence in the environment.
- IGRs have been shown to cause numerous sublethal effects, viz. larval-pupal intermediates, adultoids, increase/decrease in fecundity, transovarial effects and developmental rate as well as changes in sex ratio, diapauses and morphology.
- Insect growth regulators are categorized into three types on the basis of their mode of action, i.e. juvenile hormone analogues, ecdysone antagonists and chitin synthesis inhibitors.

- Analogues of hormones, i.e. juvenile and ecdysteroids, are being used at commercial level in integrated pest management programmes.
- Although the use of insect hormone analogues is limited, the qualities like species specificity, nonpersistence in the environment and safety to nontarget organisms make them ideal candidates for pest management programmes.
- Presently, a number of commercial IGRs are available, but there is need for exploring more IGRs to expand our knowledge regarding their chemistry and effects on insect pests, so that the use of these compounds could be expanded in integrated pest management programmes.
- Neuropeptide analogues and anti-juvenile hormone could be a bright future for insect growth regulators, if successfully commercialized.

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