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Review

Biological and Environmental Aspects of Imidazole Derivatives as Potential Insect Growth Regulators in Pest Management

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Abstract

This paper reviews the biological and environmental aspects of imidazole derivatives and their potential as insect growth regulators (IGRs). Imidazoles, known for their broad pharmacological and pesticidal properties, act on insect hormonal systems by inhibiting the biosynthesis of juvenile hormone and ecdysone, leading to developmental disruption, premature metamorphosis, or mortality. Particular emphasis is placed on the compound KK-42, which shows significant effects across several insect orders. Although commercially available imidazoles are currently registered as fungicides, their selective activity, low toxicity, and synergistic potential with other pesticides make them promising candidates for developing new insecticidal agents. The paper also discusses their environmental toxicity and compatibility with beneficial organisms, highlighting the need for further research to minimize ecological risks and promote sustainable pest management in agriculture.

Keywords: metamorphosis; hormonal disruption; inhibition; toxicity; mortality; pesticide synergism

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1. Introduction

The excessive use of synthetic pesticides has caused pest resistance and the withdrawal of many products, reducing their overall effectiveness. Globally, pests and diseases cause yield losses of up to 40% each year, resulting in economic damage exceeding USD 220 billion [1]. To maintain sustainable and profitable agriculture, new alternative protection methods are needed, integrating pesticides into IPM strategies. The ideal insecticide should be biorational—target-specific, biodegradable, and environmentally safe [2]. Biorational insecticides should effectively control insect pests. There is a clear need in today's market for insecticides that are safer and more selective. The chemical industry invested significant effort into reducing risks tied to the production and application of chemicals. These include innovative chemical processes for waste treatment and new technologies for monitoring contamination of air, water and soil [3].

Imidazole derivatives have diverse range of pharmacological and pesticidal properties, which can be further enhanced through subtle structural modifications. Azole compounds are typically used as antifungal drugs, for treatment of human diseases. OECD reports the

role of imidazole as an industrial intermediate in the production of dye intermediates, textile auxiliaries, photographic chemicals, and corrosion inhibitors [4]. Imidazole is also used in the control of fabric-feeding insects, often in combination with dl-p-fluorophenylalanine, and can act as a contact insecticide in oil-based formulations [5]. The common clothes moth larvae, *Tineola bisselliella*, which feed on wool, can be effectively controlled using azoles, namely imidazole, benzimidazole, and triazole derivatives. Same compounds are used to protect natural materials, including textiles and leather, from insect damage [6,7]. Wool fabrics treated with imidazole, either alone or in combination with boric acid, control the pest larvae of *Attagenus megatoma*, although the efficacy of imidazole is generally lower than that of boric acid, however synergistic effect is observed when the two compounds are combined [8].

In agricultural science, the use of imidazoles is associated with the development of plant protection products, where they have demonstrated their potential in the control of fungal and invertebrate pests. Imidazoles target important biological processes, either by inhibiting sterol biosynthesis in fungi or by modulating hormone regulation in insects, and they are an effective tool in IPM programs. This broad biological activity has made imidazoles the subject of intensive research, with their first commercial application linked to the development of fungicides. Compound prochloraz, introduced in 1977, was among the first imidazole fungicides developed for agricultural use. Its fungicidal activity is based on the inhibition of cytochrome P450-dependent 14α-demethylase and the disruption of ergosterol biosynthesis, against a broad spectrum of plant pathogens [9,10]. A major concern in Europe is combined application of synthetic insecticides from class neonicotinoids or pyrethroids with imidazole fungicides, since these fungicides inhibit cytochrome P450 enzymes in honey bees, enhancing the toxicity of synthetic insecticides [11]. Several fungicides based on imidazoles are still registered and permitted in European Union (EU), particularly for post-harvest treatment of fruit and for field applications against cereal and vegetable pathogens. The imidazole-based pesticides currently available on the market in the EU are registered as fungicides (Imazalil/Enilconazole) [12]. Outside the EU, several imidazole-based pesticides remain registered for agricultural use, including imazalil and prochloraz. Imazalil, classified as a WHO/PCS Class II "moderately hazardous" compound with an ADI of 0–0.03 mg/kg bw/day (FAO/WHO JMPR), is widely authorized in regions such as the United States, Australia, South Africa, and numerous countries in Central and South America [13]. WHO and EU toxicological assessments indicate that imazalil does not bioaccumulate, is rapidly metabolized and excreted, and shows no genotoxic or carcinogenic potential of concern, although it is harmful by inhalation and ingestion and strongly irritant to the eyes. Prochloraz, although no longer approved in the EU, continues to be permitted in several non-EU markets, where it is formulated and commercialized for use against a broad spectrum of fungal pathogens [13,14]. These differences reflect regional variations in regulatory criteria and risk assessment frameworks, resulting in continued global use of certain imidazole fungicides despite their withdrawal or restriction in the EU.

No imidazole compounds are currently classified as insect growth regulators (IGRs) for commercial use. Compared with other groups of insect growth regulators, imidazole derivatives have been investigated less extensively in the context of insect development, highlighting the importance of compiling and evaluating the available data. To provide a clearer overview of their potential, this review summarizes current findings on 27 structurally distinct imidazole derivatives with documented physiological effects on insects. These include members of the KK- and TH-series, imidazolium salts, diphenyl imidazolyl derivatives, and individual compounds with specific endocrine activity. Their effects have been reported across five insect orders and 23 insect species, reflecting the broad biological activity of insects to imidazole-derived structures, also the potential and limits for further

development of new imidazoles as plant protection products. By compiling biological data of imidazole derivatives with documented hormonal or developmental effects in insects, this review provides a foundation for future SAR and QSAR studies and highlights the collective potential of these compounds for the development of new IGR candidates within integrated pest management.

2. Imidazoles: Natural Derivatives with Potential in Pest Control

Imidazoles are widely known heterocyclic compounds that play an important role in medicinal chemistry. Imidazole is a planar five-membered heterocyclic ring composed of three carbon atoms and two nitrogen atoms located at positions *N1* and *N3*. The simplest parent compound, imidazole (1,3-diaza-2,4-cyclopentadiene), has the molecular formula $C_3H_4N_2$ and is soluble in water and other polar solvents. Imidazole exhibits tautomerism (Figure 1), as the hydrogen atom can migrate from one to the other nitrogen atom giving two equivalent forms (1*H*-imidazole), but can also be located at the position *C4* (4*H*-imidazole) [15].

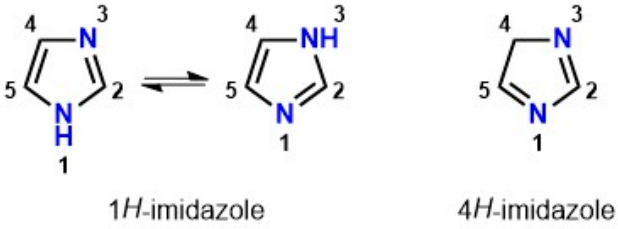

Figure 1. Tautomers of imidazole. (**Left**): two resonance structures of 1H-imidazole. (**Right**): 4H-imidazole. (Numbers denote atom numbering positions in imidazole ring).

Imidazole is an aromatic compound due to the presence of a conjugated π system with six delocalized electrons, two of which originate from the nitrogen atom bearing a hydrogen, and one from each of the other four atoms. The *C4-C5* positions of imidazole are the primary sites for modification, either through direct substitution or fusion with additional aromatic rings [16]. Their high triplet energy levels (ET1) and good carrier transport make them valuable in electronic applications [17]. It is a polar compound and can form hydrogen bonds, both intramolecular and with others. Imidazole is also amphoteric because it can behave both like acid and a base. The hydrogen on the pyrrole-like nitrogen can be donated making it acidic, while the pyridine-like nitrogen has a lone pair of electrons, making it basic [18] (Figure 2). The *N3* nitrogen from imidazole can be protonated by strong acids which leads to formation of stable crystalline imidazolium salts. Moreover, there are also partially or fully saturated imidazole derivatives (imidazolines and imidazolidines) and fused derivatives such as benzimidazoles [19]. Its high polarity and water solubility allow its occurrence in biologically important molecules. The amino acid histidine and its decomposition product histamine have the imidazole structure, as do biotin, purine and DNA bases. Similarly, the imidazole nucleus is the core structure in compounds such as cobalamin, theophylline and various alkaloids [15,20]. Imidazoles are components of numerous biologically important molecules, including the essential amino acid histidine and other compounds such as histamine, biotin, and various imidazole alkaloids. Natural imidazole alkaloids have been isolated from diverse organisms: among fungi, the best known is hercynine from mashroom *Boletus edulis*, while marine sponges such as *Geodia gigas*, *Agelas oroides*, *Leucetta* spp., *Clathrina* spp., *Leucosolenia* spp., and *Hyrtios* spp. contain numerous imidazole-based metabolites, including pyrrole-2-imidazole alkaloids such as clathrodin and oroidin [21–24]. From the seeds of garden cress, *Lepidium sativum*, a compound named lepidine was identified as the known source of dimeric imidazole alkaloids [25]. As a member of the Rutaceae family, *Pilocarpus* is recognized as the

principal plant source of pharmacologically relevant imidazole alkaloids, which include pilocarpine, isopilocarpine, pilocarpidine and pilosine, with *P. jaborandi* being particularly notable—pilocarpine accounts for 70.8% of its total alkaloid content. Moreover, nine additional imidazole alkaloids have been isolated from this genus, further underscoring its chemical diversity and biopotential [26,27]. Pilocarpine has been shown to reduce aggression toward nestmates in honey bees by modulating muscarinic cholinergic signalling, indicating that imidazole-based compounds can also influence olfaction-mediated social behaviour in beneficial insects [28].

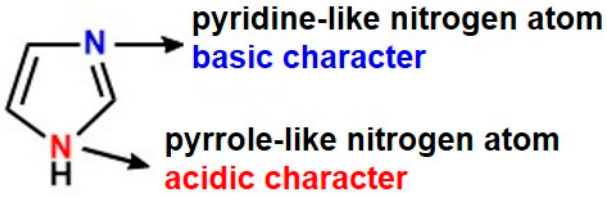

Figure 2. Amphoteric nature of imidazole (acidic and basic nitrogen atoms are coloured red and blue, respectively).

Research on derivatives of imidazole started in the 1840s. Heinrich Debus is credited with the first synthesis of imidazole in 1858. The synthesis involved the reaction of glyoxal and formaldehyde with ammonia, and the compound was initially called Glyoxaline. It was selected for commercial use due to its efficacy, cost-effectiveness, and negligible toxicity to mammals [6]. The term 'imidazole' was later introduced by the German chemist Arthur Rudolf Hantzsch in 1887 [20,29]. The biological importance of imidazole became clear when it was identified as a key component of essential biomolecules, which led to extensive research into its therapeutic potential. This discovery led to the development of imidazole-based drugs, particularly for the treatment of fungal infections. In the late 1970s, ketoconazole, a more polar imidazole derivative, represented a significant advance in antifungal therapy in humans. The introduction of this agent revolutionized the treatment of fungal infections by providing an effective and targeted approach, particularly for previously difficult-to-treat fungal diseases [16]. Besides a wide range of pharmacological activities, they exhibit antibacterial, antiviral, antitubercular, antifungal, anti-HIV, anticancer, anti-inflammatory, analgesic, anthelmintic, and other effects [16,20]. Their activity has been enhanced through minor structural alterations. This broad spectrum of activity is related to the fact that imidazole itself possesses superior pharmacodynamic properties and reduced toxicity compared to several other heterocyclic compounds, mainly owing to its structural similarity to histidine [15]. Imidazole derivatives, with their selective bioactivity and low toxicity, have proven valuable in agronomy, specifically in pest control [20]. Although they are registered for various purposes, such as fungicides and pharmaceuticals, they exhibit bioactivity against insects, indicating that the imidazole scaffold holds promising potential for pest control.

Imidazole compounds have been researched for their role as IGRs, as they can interfere with the insect hormonal system, and their insecticidal properties. They can interfere with the synthesis or action of juvenile hormones and ecdysone, which are critical for insect development and moulting. As a result, imidazole-based IGR can significantly affect the proper development of insects, resulting in immature or malformed insects that cannot reproduce.

3. Hormonal Regulation in Insects

Hormones secreted by the central neuroendocrine system regulate key developmental processes in insects, including moulting, metamorphosis, reproduction, and diapause [30,31] (Figure 3). Neuropeptides trigger developmental events such as the release of activation

hormone and juvenile hormone (JH) to regulate larval growth and reproduction. Synthetic analogues of JH (juvenile hormone analogues, JHAs or juvenoids) mimic its activity and form the basis of IGRs, a group of compounds that selectively disrupt endocrine functions and interfere with moulting and chitin synthesis [32,33].

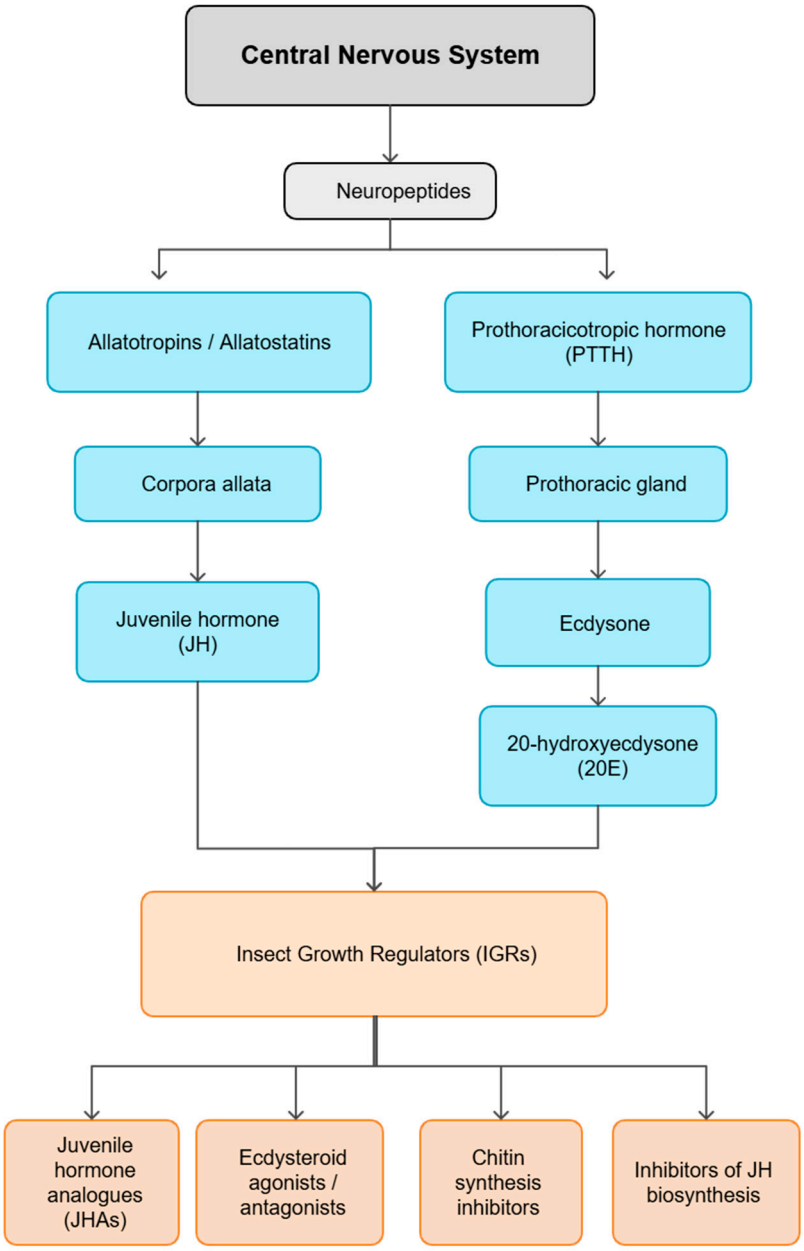

Figure 3. Hormonal regulation of insect growth and development.

The ecdysis hormone, which is produced by the prothoracic glands, controls the formation of the new cuticle and the moulting process. By preventing successful metamorphosis, IGRs keep insects in immature stages or cause sterility. They are generally selective with limited non-target effects, although resistance can develop [30,31]. Thirty-one different compounds or substances have been identified as IGRs and their activity for insect pest control has been described [31].

3.1. Juvenile Hormone

The JH is a sesquiterpenoid produced and secreted by the corpora allata under the control of neuropeptides, allatotropins and allatostatins [30]. It plays a crucial role during

moulting by preventing the expression of genes responsible for adult development, thus keeping the insect in its immature larval or nymphal stage [31,34]. When larvae reach the appropriate developmental stage, JH synthesis ceases, reducing expression of the Krüppel-homologue 1 gene and enabling metamorphosis [35]. In adult insects, JH promotes reproductive processes and regulates diapause [36]. Their application at times when natural JH is absent disrupts normal development, leading to repeated larval moulting or abnormal pupation, often producing oversized larvae. JHAs such as methoprene, hydroprene, fenoxycarb and pyriproxyfen are widely used in targeted and environmentally friendly pest management strategies [30,31,34].

3.2. Ecdysone

As a steroid hormone, ecdysone plays an essential role in the control of important developmental and physiological events in insects [37,38]. It is mainly synthesized in the prothoracic gland and converted to the active hormone 20-hydroxyecdysone (20E) in peripheral tissues [39]. The active hormone binds to the ecdysone receptor and forms a heterodimer with ultra-spiracle, initiating transcription of genes essential for moulting and metamorphosis [37]. The prothoracic gland integrates multiple signals, including hormonal and nutritional cues, to precisely control these transitions [39]. Beyond development, ecdysteroids influence reproduction, stress physiology, longevity and neuronal function [38]. Experimental application of 20E promotes ovarian maturation and oviposition in *Spodoptera frugiperda* [40]. Ecdysteroids also play a role in regulating the circadian rhythms and behaviour of adult insects [38]. Ecdysone agonists such as bisacylhydrazines induce premature and lethal moulting by activating ecdysone-regulated genes [30].

3.3. Insect Growth Regulators

Several groups of compounds have been identified as endocrine insecticides, agents that disrupt the hormonal regulation of insect growth and development: JHAs, ecdysteroid agonists and antagonists, chitin synthesis inhibitors, and inhibitors of JH biosynthesis. Although their mechanisms differ, they share a common outcome: disruption of the hormonal balance between juvenile hormone and ecdysteroids, resulting in abnormal development, sterility, or death.

JHAs mimics the insect's natural hormone, maintaining larvae in the immature stage and preventing metamorphosis; well-studied examples include methoprene, pyriproxyfen, hydroprene, and fenoxycarb. Ecdysteroid agonists and antagonists stimulate or suppress ecdysteroid activity responsible for moulting, such as tebufenozide, methoxyfenozide, and halofenozide as agonists, and azadirachtin or certain imidazole derivatives as inhibitors of ecdysteroid biosynthesis or signalling. Chitin synthesis inhibitors (benzoylureas) indirectly disrupt hormonal control by preventing chitin formation and causing failed moulting, including diflubenzuron, lufenuron, triflumuron, and hexaflumuron [30,31].

Inhibitors of JH biosynthesis, or anti-JH hormones, such as imidazole derivatives, precocene, and certain fluorinated ketones, block enzymes involved in JH production, leading to premature metamorphosis or developmental arrest. Imidazoles may also affect ecdysteroid biosynthesis depending on the insect species and developmental stage [41]. Natural endocrine disruptors, including azadirachtin, phytoecdysteroids, and flavonoids, can mimic or inhibit insect hormones and cause developmental abnormalities. Interference with JH biosynthesis and signalling is a particularly effective mechanism affecting processes such as metamorphosis, reproduction and diapause. These compounds have been studied in different insect orders, revealing different physiological effects and emphasizing their potential as selective pesticidal agents.

4. Imidazole Derivatives: Effects on Insect Development

Imidazole derivatives have not been sufficiently investigated as IGRs in agricultural science, with most research focusing on 1-benzyl-5-[(E)-2,6-dimethyl-1,5-heptadienyl]imidazole, commonly known as KK-42. This derivative can be regarded as a benchmark compound within imidazoles as IGRs. In addition to inhibiting juvenile hormone (JH) and ecdysone biosynthesis, KK-42 reduces ecdysteroid levels in the haemolymph, delaying larval ecdysis, ovarian growth, and adult emergence in freshly ecdysed silkworms [42]. Other imidazole derivatives have not received as much attention and their potential as IGRs remains largely unexplored. While KK-42 has been extensively studied in the insect order Lepidoptera, it also affects the development and reproduction of insects from the orders Orthoptera, Coleoptera, and Diptera.

4.1. Lepidoptera

Bombyx mori, silkworm, an economically important species, is often used as a model organism for studies on IGR. Several imidazole derivatives exhibit strong insect growth regulatory activity by disrupting juvenile hormone and ecdysteroid pathways in *B. mori*. At a dose of 3 µg per larva, KK-42 increased the pupation rate to 94% in *B. mori*, indicating that metamorphosis was occurring earlier than usual. When the amount exceeded 4 µg per larva, mortality increased and it also led to a reduction in cocoon and shell weight [41]. Although KK-42 exhibited stronger activity, in the same study another compound was tested KK-22 which also induced precocious metamorphosis [43,44]. This extension enables a longer feeding period and more extensive cocoon formation, which directly contributes to a higher silk yield. Another study confirmed developmental changes in *B. mori*, showing that larval duration was shortened by four days, which improved silk quality and provided economic advantages for sericulture [45]. In *Bombyx mandarina*, oxygen consumption in KK-42–treated pupae was very low compared to the control but gradually increased around 35–37 days after treatment. An increase in oxygen consumption was observed approximately 12 h after the application of 20-hydroxyecdysone, indicating the continuation of metamorphosis [46].

Another derivative, l-Isobutyl-5-(4-phenoxyphenyl)imidazole (KK-98) induced early metamorphosis when applied at higher concentrations [47,48]. Early metamorphosis or moult arrest in *B. mori* larvae has also been observed after treatment with KK-51, KK-71, KK-42, KK-83, KK-85, KK-110, KK-135, and KK-98, demonstrating that multiple KK-series imidazole derivatives interfere with normal endocrine regulation and significantly alter silkworm development [47,49].

Topical treatment of *B. mori* larvae at the pre-final larval instar stage with KS-175 resulted in delaying metamorphosis and moulting lasting over 20 days, indicating a potent inhibition of development. Subsequent tests showed that KS-175 irreversibly impaired ecdysteroid bio-synthesis in the prothoracic glands [50].

In maize pest *Ostrinia nubilalis*, the European Corn Borer, KK-42 caused delayed larval growth and development and premature spermiogenesis in the fourth larval instar without diapause [51]. In the same study, KK-42 caused a significant decrease in oxygen consumption during the pupal stage of *O. nubilalis*, which lasted about 40 days. KK-42 also delayed the termination of diapause in *Lymantria dispar japonica*, *Antheraea pernyi* and *Helicoverpa zea*, *Antheraea yamamai*, *Helicoverpa armigera* and accelerated development in *H. zea* and *O. nubilalis* when applied to larvae prepared for diapause [51–55]. The impact of KK-42 on *H. zea* pupal diapause depended on both the dosage and the insect developmental stage.

4.2. Ortoptera

In Orthopterans, KK-42 had minimal effects on larval development in *Locusta migratoria*, the African migratory locust, but significantly disrupted oocyte and egg development in adult females, without affecting ovarian ecdysteroid synthesis [56,57]. Similarly, in *Gryllus bimaculatus*, the field cricket, KK-42 was found to modulate ecdysteroid production in the ovaries and abdominal integument, while ketoconazole, a synthetic imidazole, also inhibited steroidogenic pathways [58]. Ketoconazole is still approved for use in human and veterinary medicines in many countries, mainly in topical formulations such as creams and shampoos, but it is not approved for use as an agrochemical. KK-42 strongly inhibited ecdysteroid production in the prothoracic glands of *Schistocerca gregaria*, the desert locust, larvae and reduced hatching success when applied to eggs, resulting in dose-dependent embryonic mortality. However, injections into adult females had no effect on the deposition of ecdysteroids in the eggs, nor on the lifespan or fertility of treated individuals [59].

4.3. Coleoptera

In Coleopterans, KK-42 strongly inhibits ecdysteroid biosynthesis and lowers hormone levels in both pupae and eggs in *Tenebrio molitor*, mealworms, impairing insect development and reproduction. Topical application to pupae resulted in significant disruption of pupal development, reduced hatching rate of adults and changes in ecdysteroid titres, by delaying and suppressing maximum hormone levels during metamorphosis. In contrast, other IGRs not from imidazole groups, RH-0345 (halofenozide), a bisacylhydrazine ecdysteroid agonist, increases ecdysteroid production, particularly 20-hydroxyecdysone, and can partially counteract the effects on reproduction caused by KK-42 [60,61]. Topical application of KK-42 and KK-22 to *Tribolium freemani* increased larval mortality from 60% to 84% across the tested dose range of 100 to 1000 ppm, while pupation was completely inhibited at all tested doses. The higher doses of both compounds showed a stronger effect in the topical assays on *T. freeman* [62].

4.4. Blattodea

l-Isobutyl-5-(4-phenoxyphenyl) imidazole also known as KK-98, significantly inhibits the biosynthesis of JH III in the corpora allata of *Diploptera punctata*, showing greater efficacy than KK-42, KK-51, KK-71, KK-83, KK-85, KK-88, KK-96 [47].

4.5. Diptera

KK-42 caused malformations in the spiracles and mandibles of *Sarcophaga bullata* larvae, the grey flesh fly, which became abnormally sclerotized, leading to unsuccessful moulting and subsequent larval mortality. In contrast, clotrimazole, another imidazole compound, under the same experimental conditions did not affect the same species [63]. KK-42 accelerated development in *Sarcophaga crassipalpis* when applied to larvae prepared for diapause [52]. At a concentration of 2000 ppm, KK-110 caused 100% mortality in *S. bullata* larvae, while at 500–1000 ppm, larval development time did not differ from the control, but puparial weight was reduced [63]. Since mosquito control is increasingly hindered by widespread insecticide resistance, imidazole derivatives from the TH-series have gained attention because they inhibit JH biosynthesis in Diptera, particularly in *Aedes aegypti* larvae, an important vector of human arbovirus diseases [64]. The imidazole salt C18MlmCl was tested against four species of mosquitoes. It proved to be highly effective in controlling *A. aegypti* and *Aedes albopictus*, since it caused persistent toxicity to the larvae even after two months of environmental exposure. The larvicidal effects of the same imidazole salt were observed against *Culex pipiens fasciatus* larvae. This compound caused 100% mortality at 1 ppm and 88% mortality at 0.5 ppm, emphasizing potential of imidazole

salt for effective vector management at low concentrations [6,65,66]. In another study, two imidazole salts were tested against *Culex quinquefasciatus*, and both were effective, however C18MImCl exhibited stronger larvicidal potency (LC_{50} = 3.175 µg/mL) compared to C16MImMeS (LC_{50} = 4.613 µg/mL) [67].

4.6. Hemiptera

Compounds KK-110 and KK-135, at a dose of 100 µg, showed different effects on the mortality of *Oncopeltus fasciatus*, true bug. KK-110 caused 100% mortality within 48 h, whereas KK-135 induced delayed mortality ranging from 35% to 100%. While compound KK-98 at doses of 10 µg and 50 µg caused 100% delayed mortality [49]. Imidazole derivatives namely from 5a to 5j caused mortality of larvae and adults of *Aphis craccivora*, aphid at all applied concentrations (1.23–3.05 mg/L for larvae; 2.98–7.01 mg/L for adults). Among tested imidazoles, compound 5g was notable, with an LC_{50} value of 1.15 mg/L, comparable to the reference insecticide imidacloprid (1.06 mg/L), which is attributed to the presence of a fluorine atom enhancing its biological efficiency [68].

KK-series imidazole derivatives possess higher lipophilicity due to their terpenoid side chains, which likely facilitate cuticular penetration more efficiently and enhance in vivo activity compared to the less lipophilic TH-series analogues, which have shorter and often more saturated side chains, sometimes containing polar functional groups (Figure 4).

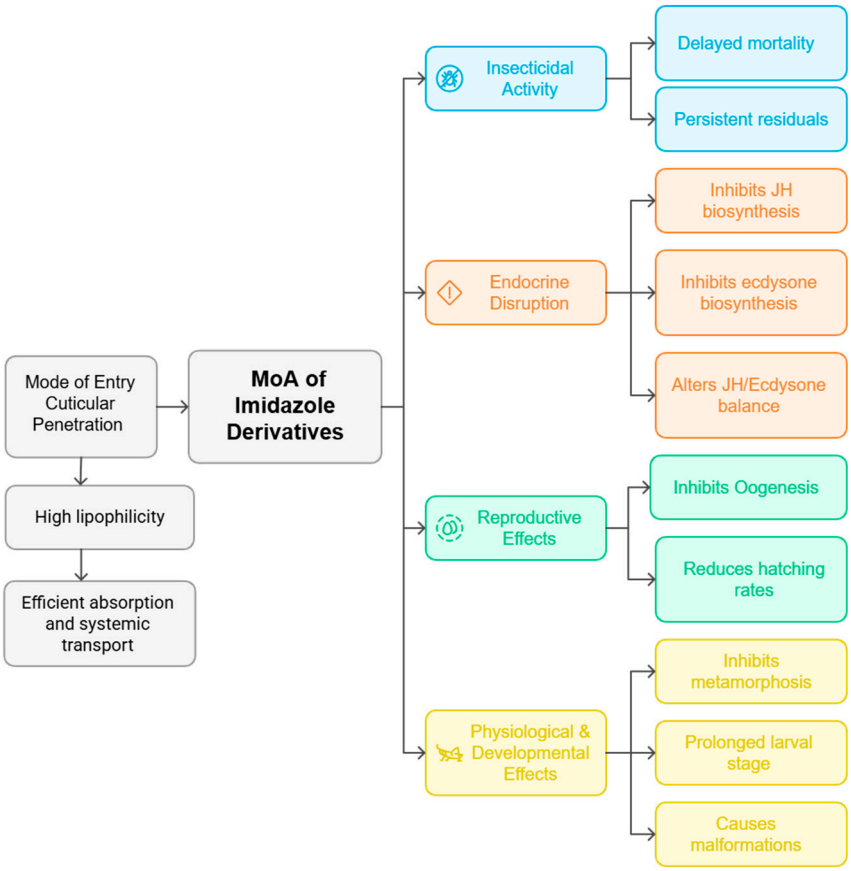

Figure 4. Mode of entry and mechanism of action (MoA) of imidazole derivatives in insects.

The following table provides an overview of the best-known imidazole derivatives that have shown significant bioactivity, and have gained long-term importance for practical applications (Table 1).

Table 1. Biological effects and mechanisms of action of imidazole derivatives in insects.

Imidazole Derivative	Chemical Formula	Main Mechanism of Action	Order	Insect Species	Biological Effect/ Application Potential
KK-42	1-benzyl-5-[(*E*)-2,6-dimethyl-1,5-heptadienyl]imidazole	Inhibition of ecdysteroid synthesis/metamorphosis Acceleration of development Regulation of diapause Reproductive disruption Inhibition of juvenile hormone synthesis	Lepidoptera	*Antheraea pernyi*	Delays diapause termination [52]
				Antheraea yamamai	Terminates embryonic diapause [54]
				Bombyx mori	Induces precocious pupation; prolongs fourth instar [41,45]
				Bombyx mandarina	Blocks pupal–adult metamorphosis; reduces respiratory activity [46]
				Helicoverpa armigera	Induces precocious diapause termination in pupae [55]
				Helicoverpa zea	Increases diapause incidence; delays diapause termination [52]
				Lymantria dispar japonica	Increases diapause incidence, delays diapause termination [52,53]
				Ostrinia nubilalis	Delays growth and moulting; induces precocious pupation [51]
			Orthoptera	*Gryllus bimaculatus*	No data for biological effects [58]
				Locusta migratoria	Prolongs final instar; disrupts oocyte and egg development [56,57]
				Schistocerca gregaria	Reduces hatching success; causes embryonic mortality [59]
			Diptera	*Sarcophaga bullata*	Lethal disturbances in preecdysial processes [63]
				Aedes aegypti	No data for biological effect [64]
			Coleoptera	*Tenebrio molitor*	Delays pupal development and reduces adult emergence [61]
				Tribolium freeman	No effect on pupation; causes larval mortality [62]
			Blattodea	*Diploptera punctate*	No data for biological effects [47]

Table 1. *Cont.*

Imidazole Derivative	Chemical Formula	Main Mechanism of Action	Order	Insect Species	Biological Effect/ Application Potential
KK-98	1-isobutyl-5-(4-phenoxyphenyl)imidazole	Disruption of juvenile hormone regulation Inhibition of ecdysteroid synthesis	Lepidoptera	*Bombyx mori*	Induced precocious metamorphosis [48]
			Blattodea	*Diploptera punctate*	No data for biological effects [47]
			Hemiptera	*Oncopeltus fasciatus*	Delayed mortality [49]
KK-22	1-citronellyl-5-phenylimidazole	Inhibition of juvenile hormone synthesis	Blattodea	*Diploptera punctate*	No data for biological effects [47]
			Coleoptera	*Tribolium freeman*	No effect on pupation; causes larval mortality [62]
			Lepidoptera	*Bombyx mori*	Induces precocious pupation; prolongs fourth instar [41,43,45]
KK-51	1-citronellyl-5-(2-ethoxyphenyl)imidazole	Inhibition of juvenile hormone synthesis	Lepidoptera	*Bombyx mori*	Induces precocious metamorphosis [47]
			Blattodea	*Diploptera punctate*	No data for biological effects [47]
KK-71	1-citronellyl-5-(2-benzyloxyphenyl)imidazole	Inhibition of juvenile hormone synthesis	Lepidoptera	*Bombyx mori*	Induces precocious metamorphosis in larvae [47]
			Blattodea	*Diploptera punctate*	No data for biological effects [47]
KK-110	5-(2-ethoxyphenyl)-1-neopentylimidazole	Inhibition of juvenile hormone synthesis Inhibition of ecdysteroid synthesis	Lepidoptera	*Bombyx mori*	Induces precocious pupation [47,49]
			Diptera	*Neobellieria bullata*	Mortality [63]
			Hemiptera	*Oncopeltus fasciatus*	Acute toxicity [49]
KK-175	1-(4-phenoxyphenoxypropyl)imidazole	Inhibition of ecdysteroid synthesis	Lepidoptera	*Bombyx mori*	Complete inhibition of moulting [50]
KK-135	I-neopentyl5-(4-chlorophenyl)imidazole	Inhibition of ecdysteroid synthesis	Hemiptera	*Oncopeltus fasciatus*	Delayed mortality [49]
			Lepidoptera	*Bombyx mori*	Induces precocious metamorphosis [47,49]
KK-83	1-*sec*-butyl-5-[(*E*)-2,6-dimethyl-1,5-heptadienyl]imidazole	Inhibition of juvenile hormone synthesis	Blattodea	*Diploptera punctate*	No data for biological effects [47]

Table 1. *Cont.*

Imidazole Derivative	Chemical Formula	Main Mechanism of Action	Order	Insect Species	Biological Effect/ Application Potential
KK-85	1-cyclohexyl-5-[(*E*)-2,6-dimethyl-1,5-heptadienyl]imidazole	Inhibition of juvenile hormone synthesis	Blattodea	*Diploptera punctate*	No data for biological effects [47]
KK-88	1-pentyl-5-[(*E*)-2,6-dimethyl-1,5-heptadienyl]imidazole				
KK-96	1-isobutyl-5-(3-geranyloxyphenyl)imidazole				
TH- series	1,5-disubstituted imidazoles	Inhibition of juvenile hormone synthesis, methyl farnesoate	Diptera	*Aedes aegypti*	No data for biological effect [64]
C_{18}MImCl	1-n-octadecyl-3-methylimidazolium chloride	Disrupts the midgut epithelium	Diptera	*Aedes aegypti*	High mortality; disrupts physiological processes (midgut damage) [65]
C_{16}MImMeS	1-n-hexadecyl-3-methylimidazoliummethanesulfonate				
C_{18}MImCl	1-methyl-3-octadecylimidazolium chloride	Disrupts the midgut epithelium	Diptera	*Aedes aegypti*	High mortality; disrupts physiological processes (midgut damage) [66]
		Mechanism unknown	Diptera	*Culex quinquefasciatus*	High mortality [67]
		Disrupts the midgut epithelium	Diptera	*Aedes albopictus*	High mortality; disrupts physiological processes (midgut damage) [66]
Imidazole	$C_3H_4N_2$	Mechanism unknown; presumed metabolic interference (histamine antagonist activity)	Diptera	*Culex pipiens fasciatus*	High mortality [6]
C_{16}MImMeS	1-hexadecyl-3-methylimidazoliummethanesulfonate	Mechanism unknown	Diptera	*Culex quinquefasciatus*	High mortality [67]
5a-5j	diphenyl imidazolyl dimethylpropanamine derivatives	Mechanism unknown	Hemiptera	*Aphis craccivora*	High mortality of nymphs and adults [68]
Cetoconazole	$C_{26}H_{28}Cl_2N_4O_4$	Inhibition of cytochrome P-450	Orthoptera	*Gryllus bimaculatus*	No data for biological effects [58]

4.7. Imidazole Derivatives: Environmental Toxicity, Effects on Vertebrates, and Compatibility

Although IGR compounds are generally safer for non-target organisms and the environment, they can induce resistance in target insect populations, limiting their efficacy [31]. Compared to other synthetic insecticides, JHAs has a better toxicological profile. Although JHAs specifically target pests, their mechanisms of action and potential side effects must be thoroughly analyzed to ensure safety and efficacy in plant protection. It is also evident that use of JHAs can induce the formation of additional, larger larval stages with extended lifespan, potentially leading to greater crop damage [30]. Imidazoles share the selective and low-toxicity profile of JHAs, but not their biological effects. Available studies have focused on their endocrine-disrupting activity in insects, with no comprehensive data on the environment and mammals. At concentrations that affect insects, they did not exhibit high acute toxicity but rather a specific hormonal effect.

Imidazole derivatives show toxicological effects in mammals, mostly related to endocrine disruption via cytochrome P450 inhibition. Their adverse effects are primarily associated with endocrine disruption resulting from cytochrome P450 inhibition. Antifungal imidazole drugs, clotrimazole, econazole and ketoconazole are the most investigated imidazoles for their potentials in human cancer treatment. Bifonazole and miconazole are also reported to have antitumor efficacy in several cancer types [69]. Some pyrrole–imidazole compounds can bind vertebrate, including human, telomeric DNA (TTAGGG) with very high specificity, as shown for derivative TH59 in HeLa cells. This demonstrates that imidazole-based molecules are capable of interacting directly with mammalian genomic DNA [70].

Although these findings indicate that some imidazole derivatives can affect mammalian endocrine or metabolic pathways, comprehensive toxicological profiles for most IGRs from KK- and TH-series compounds are not available.

Toxicological report indicates the acute oral toxicity of imidazole in rats ranges from 220 to approximately 970 mg/kg body weight, with the lowest reported LD_{50} value being 220 mg/kg, while in mice the LD_{50} range is considerably higher, from 880 to 1880 mg/kg. Available pharmacokinetic data and reports from occupational exposure to imidazoles (up to 750 mg orally and 250 mg by injection) do not indicate acute or subchronic toxicity in humans, with the most severe documented effect being mild skin irritation following direct contact [71].

Most toxicological studies have been conducted on imidazole compounds with fungicidal bioactivity, as they were commercially available only. Fungicide prochloraz is the most extensively studied compound in this context and induces antiandrogenic and developmental effects in rats, including impaired steroidogenesis and feminisation of male offspring. Similar mechanisms have been reported for antifungal drug ketoconazole in a dose-dependent manner [72,73]. λ-cyhalothrin and prochloraz when applied together increase the toxicity of insecticide in honey bees, this is because prochloraz shuts down the cytochrome P450 pathway that would otherwise break down the insecticide letting λ-cyhalothrin linger longer and become more toxic, to the bees [74]. Imazalil is a fungicide that is allowed for field application and for the treatment of cereal seeds in postharvest treatment. Only a few toxicological studies have assessed the potential environmental effects of imazalil and its impact on organisms. Imazalil caused dose-dependent DNA damage and reduced larval mobility and pupation in fruit fly, *Drosophila melanogaster*, showing clear genotoxic and behavioural effects [75,76]. This pesticide can cause morphological anomalies and locomotion changes in fish (*Danio rerio*), but did not cause immediate death of the earthworm *Eisenia andrei* after exposure [77]. The maximum residue limits for only commercially available imidazole in EU (imazalil) vary depending on the crop, with values up to 5 mg/kg for citrus fruits and 0.05 mg/kg or lower for most other commodities, according

to EU Regulation (EC) [78]. Although imazalil shows moderate residue limits compared to other pesticides, its classification as an imidazole derivative with known endocrine-related activity highlights the need for continued toxicological assessment, particularly regarding potential effects on hormonal pathways in non-target organisms.

Triflumizole (TFZ) is a broad-spectrum imidazole fungicide with protective and curative actions. Rapid photolysis and high risk to the aquatic environment limit its application [79]. It affects photosynthesis-related gene expression and pigment content to freshwater green algae *Chlorella vulgaris* [80]. Prenatal TFZ exposure promotes the formation of fat cells and increases the amount of adipose tissue in mice [81]. Furthermore, TFZ inhibits the biosynthesis of strigolactones and stimulates seed germination. TFZ induced also severe dwarf phenotype in treated rice as a side effect [82]. This compound is bioactive on insects as well, it greatly increased the toxicity of synthetic insecticides acetamiprid, thiacloprid, dinotefuran and copper to honey bees, while it had only a minor effect on imidacloprid [82,83]. Thiobendazole is used as a fungicide on seed potatoes, apples, pears and citrus, and against helminthic parasites in animals. It is considered to meet the criteria for endocrine disruption in humans for the thyroid (T)-modality [84]. Fenamidone is a foliar fungicide on potatoes and tomatoes that is not approved in the EU Regulation [85] due to its toxicity to freshwater fish and aquatic invertebrates [86]. Thiabendazole caused prolonged metamorphosis and delayed pupation in *Pemphredon fabricii*, particularly in individuals previously exposed to agrochemicals, indicating a synergistic effect. Carbendazin is a fungicide, not allowed in EU since it was reported as a reproductive/developmental toxicant. Also, it is moderately toxic to honey bees (at rates 0.25 and 0.75 mg/g) [87] and most aquatic organisms, as well as highly toxic to earthworms [88], but it significantly reduces the activity of P450 enzymes and inhibits the expression of the hymenoptaecins and apidaecin genes in honey bees thereby impairing immune and detoxification functions, which may increase the susceptibility of bees to pathogens and insecticides [89]. Imidazole fungicides show varying interaction with other beneficial invertebrates, namely entomopathogenic nematodes (EPNs), altering their survival and infectivity. Prochloraz and TFZ are compatible with EPNs, while thiabendazole and carbendazim reduce nematode survival and infectivity re reviewed previously [90].

The use of prochloraz was prohibited in the EU from 2021 [91] since studies have confirmed that it inhibits fetal steroidogenesis, alters androgen metabolism, causing feminisation of male rat offspring [92,93]. According to the U.S. EPA TSCA Inventory, imidazole (CAS 288-32-4) is listed as an active substance, and in New Zealand it is permitted for use under the relevant EPA Group Standards. In the UK, the fungicide cyazofamid is approved, as confirmed by the HSE's Register of Approved Active Substances, while the PPDB database also lists the substance prochloraz as approved for use in Morocco [14,94].

5. Future

This review proved potential of imidazole derivatives as IGRs. Future studies on imidazole derivatives should aim to develop new analogues with better selectivity, stability, and lower impact on non-target organisms. Imidazoles have shown clear, dose- and insect stage-dependent insecticidal activity, mainly by interfering with JH and ecdysteroid biosynthesis, which leads to developmental arrest, premature metamorphosis, or death in insects. Importantly, several imidazole derivatives exhibit both contact and oral activity, which represents an additional advantage for their potential use in practical pest management. Commercial imidazole fungicides, particularly imazalil, are formulated globally as EC, LS and SL preparations, which allow their use in post-harvest treatments and field applications in many regions outside the EU, including Australia, South Africa, the United States, and several countries in Central and South America. Their high lipophilicity in-

creases penetration through the cuticle and overall potency, but it may also contribute to bioaccumulation and stronger synergistic effects when combined with other insecticides or fungicides. Even though they have proven effective as insecticidal agents and synergists, their wider agricultural use is still limited as commercial imidazole-based insecticides are not available, also their incomplete toxicological data and possible effects on beneficial species. Several imidazole derivatives show poor water solubility, which limits their compatibility with standard agricultural formulations and reduces their biological performance [73]. Prochloraz is a representative example: to improve its stability and efficacy, it often needs to be incorporated into advanced formulations such as cyclodextrin complexes or nano-based delivery systems. In its unmodified form, the compound can be less stable and display weaker biological activity. These formulation challenges illustrate why many imidazole-based compounds require technological modification before they can be applied effectively in agricultural settings. In some imidazole derivatives, such as thiabendazole, rapid metabolic degradation leads to a short biological half-life, which limits the duration of their activity despite their broad-spectrum efficacy [95]. KK-42 is not commercially formulated, and therefore no registered product examples exist. However, based on its physicochemical characteristics, KK-42 would likely be compatible with typical fungicidal formulations such as EC, SC or WG. Its reported dual fungicidal and IGRs effects suggest that future studies could examine whether controlled-release or encapsulated systems may provide advantages in stability or selective delivery. IGRs employ more specialized delivery methods designed to optimize activity on early insect developmental stages. These include microencapsulation, oil-based dispersions, controlled-release granules, and nanoemulsions [96–98]. Such systems can prolong the effective life of the active ingredient, reduce volatility or photodegradation, and allow targeted action on larvae or pupae. Further research should focus on balancing lipophilicity and biodegradability, and on evaluating combined applications with entomopathogens or selective insecticides to improve efficacy while reducing environmental risk. With biological data available in this review for at least 27 imidazole derivatives, future studies should use this growing dataset to establish more precise SAR/QSAR models that can guide the rational design of new more selective and environmentally compatible IGR candidates [99].

6. Conclusions

We have provided an overview of imidazole derivatives and their effects on insects, emphasizing their chemical nature, biological activity and importance in crop protection. Examples such as KK-42 and related derivatives show strong effects on insect JH and ecdysteroid pathways. By demonstrating potent, hormone-targeted effects in key agricultural pests, including lepidopteran defoliators, coleopteran storage pests and dipteran disease vectors, imidazole derivatives show strong potential as tools for pest management, offering selective disruption of insect development in crops such as maize, vegetables, and stored grain. However, it is important to note that imidazole can significantly increase the toxicity of neonicotinoid and pyrethroid insecticides by inhibiting cytochrome P450 detoxification in beneficial insects, which highlights the need for careful consideration of combined use.

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