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Pyrrole and pyrrolidine analogs: The promising scaffold in discovery of pesticides

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ABSTRACT

Pyrrole is a heterocycle with four carbon atoms and a nitrogen atom, which is extensively used in the pesticide and pharmaceutical industries. In addition, it has a series of analogs such as pyrrolidine, pyrroline, and pyrrolidone. Pesticides containing pyrrole and its analogs have been formally marketed as fungicides, including fenpiclonil, fludioxonil, the insecticide chlorfenapyr, and the herbicide fluorochloridone. In this paper, we analyze the structure-activity relationships (SARs) of pesticides containing these structures. We summarize the characteristics possessed by the most highly active pyrrole and its analogs and provide an overview of research on pyrrole compounds with insecticidal, antimicrobial, herbicidal, and antiviral properties in the past 20 years. It is hoped to provide ideas for the development and design of this type compounds in pesticides and to assist researchers in this area.

1. Introduction

Pyrrole, a heterocyclic ring with a nitrogenous five-membered structure and the molecular formula C_4H_5N, is a fundamental heterocycle in biochemistry. Its flat, electron-rich ring is highly susceptible to electrophilic attack, allowing it to react with other biomolecules through hydrogen bonding and π-π stacking interactions [1]. This fundamental structure is present in numerous chemicals, natural products, and various biomolecules. Moreover, there are analogs like pyrrolidine that lack aromaticity in comparison to pyrrole. The distinct bond angles and lengths indicate the planarity of pyrrole's 2D structure and the three-dimensional nature of pyrrolidine. Research has found that [2] 70% of natural products are non-flat and represent an interesting resource for designing new synthetic molecules [3]. Furthermore, pyrroline exhibits excellent potential for application in synthesis, allowing for oxidation to generate pyrrole and reduction reactions to produce pyrrolidine, as well as facilitating additional olefin functionalization through addition reactions. Additionally, pyrrolidone has been effectively employed in the synthesis of various alkaloids [4] and serves as a suitable precursor for unique amino acids like statin and its derivatives [5].

The early investigations into the biological activity of pyrrole compounds primarily centered on active compounds derived from natural products [6], such as nicotine (Fig. 1) extracted from plants [7]. It is a non-systemic insecticide that binds to the cholinergic acetylcholine nicotinic receptor in the nerve cells of insects, leading to continuous firing of the neuroreceptor. Ryanodine (Fig. 1), found in the plant *Ryania speciosa* [8], can trigger massive muscle control actions in a sub-conductance state. However, at micromolar concentrations, it can also lead to loss of muscle function by reducing the conductance and excitability of ryanodine acceptor. D-AB1 (Fig. 1) acts as a defense factor against herbivorous insects [9]. There is also a polyhydroxylated pyrrolidine compound **1** (Fig. 1) extracted from *derris* spp. and compound **2** (Fig. 1) which has a similar structure to compound **1**, isolated from *Angylocalyx boutiqueanus*. These compounds exhibit a distinct impact on nematodes [10,11]. Compounds **3** and **4** (Fig. 1) extracted from plants, have shown antifeedant activity against lepidopteran insects [12]. Compounds **5–8** (Fig. 1) extracted from sponges or insects, can be lethal and evade a large number of insects [13-15]. Pyrrole ring-containing antibiotic compounds **9–12** (Fig. 1), derived from microorganisms and microbial metabolites have varying degrees of antibacterial and insecticidal activity [16-19]. Further research has resulted in many structural modifications of natural products and advancements, leading to the creation of new varieties of potent pesticides that contain pyrrole and its analogs. In the medical field, pyrrole compounds are also utilized in a diverse array of applica-

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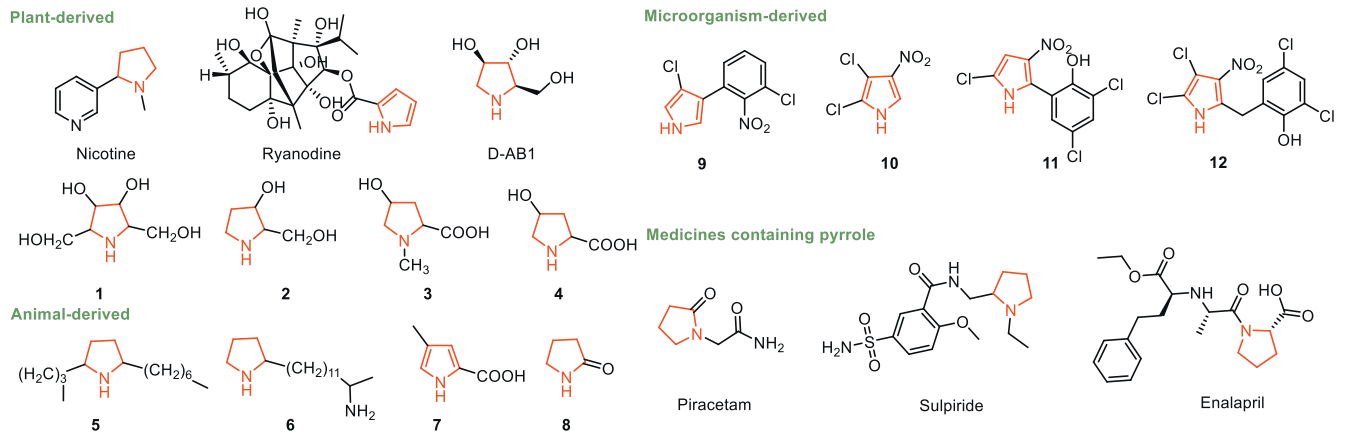

Fig. 1. Pyrrole and its analogs natural biological derive and medicines.

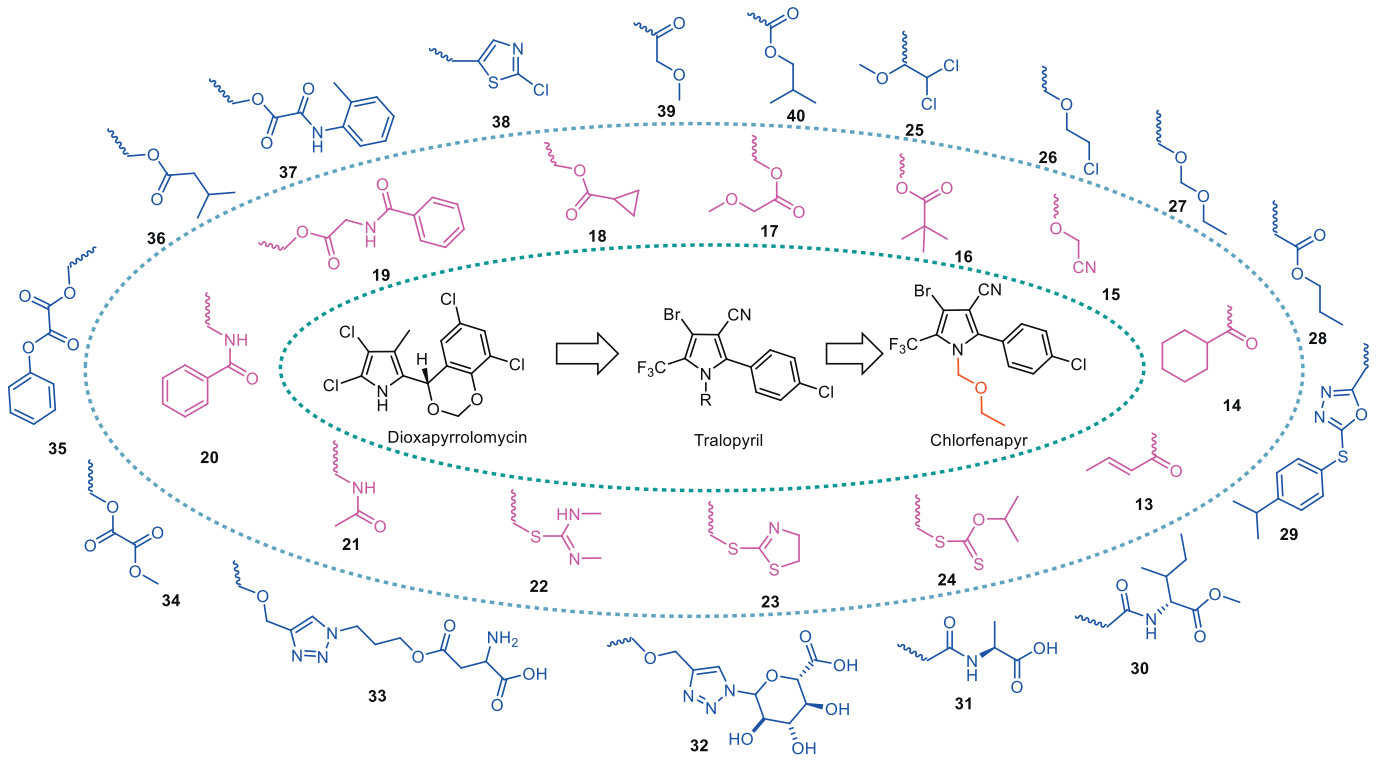

Fig. 2. Pyrrole insecticidal molecules derived from tralopyril.

tions, such as piracetam (Fig. 1) for the treatment of memory loss [20], the antipsychotic drug sulpiride (Fig. 1) [21], and enalapril (Fig. 1) for the treatment of high blood pressure [22].

Before this, we have learned the biological activities of pesticides containing spiro[23,24] and indole [25,26] in our work. While many of them contain pyrrole-like heterocycles, it has recently been discovered that rings containing pyrrole and its derivatives alone also demonstrate exceptional biological activity. This paper aims to provide a thorough examination of pesticides that contain pyrrole and its analogs, in order to offer valuable insights for future research in similar areas.

2. Insecticidal activity

2.1. Pyrrole

Tralopyril (Fig. 2) is a 2-arylpyrrole compound modified from dioxapyrrolomycin (Fig. 2) isolated from a strain of *Streptomyces* spp. It is known for its impressive insecticidal and acaricidal properties. The mechanism of action involves acting as a decoupling agent, inhibiting oxidative phosphorylation, and disrupting the conversion of adenosine diphosphate (ADP) to adenosine triphosphate (ATP) within the mitochondria. This disruption prevents insects from producing energy, ultimately leading to their demise [27]. However, tralopyril can cause severe toxicity in plants [28]. The public was later informed about chlorfenapyr (Fig. 2). When the *N*-ethoxymethyl group is oxidatively removed after entering insect bodies, the pesticide is activated, releasing tralopyril to exert its toxicity [29]. However, chlorfenapyr also exhibits high toxicity to certain environmental organisms, has a long half-life in specific environments, and shows acute oral toxicity to male rats with an LD_{50} of 441 mg/kg [30]. In order to enhance its biological properties and reduce resistance, researchers have conducted thorough investigations and made significant alterations to this derivative. The main area of structural modification has centered around replacing the group on the N of the pyrrole. For example, the early

N-acylated derivatives **13** and **14** (Fig. 2) [31], at 100 mg/L, showed 100% lethality against *Heliothis virescens* (*H. virescens*), *Empoasca abrupta* (*E. abrupta*), and *Spodoptera eridania* (*S. eridania*). They were also effective against *Blattella germanica*, among others. In addition, direct oxygenation with tralopyril N is also used, resulting in the *N*-oxo compound **15** (Fig. 2) demonstrated remarkable insecticidal properties against *S. eridania* and *H. virescens*, while compound **16** (Fig. 2) was effective against *Aphis fabae* (*A. fabae*) and *S. eridania* [32]. More importantly, compounds that involve connecting *N*–oxoalkyl groups, such as *N*-substituted carboxylic acid ester derivative **17** (Fig. 2) [33]; and cycloalkyl carboxylic acid ester derivative **18** (Fig. 2) [34], have excellent insecticidal and acaricidal activity. Further derived *N*-substituted pyrrole derivatives of aminoalkyl carboxylic acid esters such as compound **19** (Fig. 2) [35] showed good insecticidal activity against *S. eridania*, *E. abrupta* and *H. virescens*. Convert O in alkoxy group to N and S, N-amide pyrrole derivatives **20** and **21** (Fig. 2) also have good insecticidal and acaricidal activity [36]. *N*-Thioalkyl compounds **22–24** (Fig. 2) which have heteroatoms or heterocyclic groups introduced, displayed outstanding efficacy against larvae of *H. virescens*, *S. eridania* and *E. abrupta*. Compound **24** showed excellent activity against the adults and eggs of *Tetranychus urticae* (*T. urticae*) and *E. abrupta*, with a lethality rate of 100% at 10 mg/L [37].

There have been many studies conducted on structural modifications to tralopyril 1-N, and some recent findings have been noted. For example, Liu *et al.* introduced alkoxy groups substituted with halogenated hydrocarbons on 1-N. At 0.25 mg/L, compound **25** (Fig. 2) showed 93.3% insecticidal activity against *Mythimna separata* (*M. separata*) and 100% insecticidal activity against *A. fabae* and *T. urticaes* at 500 mg/L and against *M. separata* (LC_{50} = 31.67 mg/L) [38]. Following the substitution of alkoxy groups with halogenated hydrocarbons, compounds **26** and **27** (Fig. 2) showed inhibitory activities on par with chlorfenapyr against *M. separata* and *T. urticaes*. However, the introduction of the N-alkyl group reduced DNA damage, and compound **26** has low acute toxicity to mammals (LD_{50} = 4640 mg/kg, much lower than that of chlorfenapyr's 626 mg/kg). With its high efficiency, broad-spectrum effectiveness, crop safety, and low toxicity to humans and animals, this product is making strides towards industrialization [39]. In addition, Zhou introduced acetic acid [40], oxadiazole [41], and amino acid [42] on 1-N, compounds **28–31** (Fig. 2) exhibited remarkable insecticidal activities against *Caenorhabditis elegans* (*C. elegans*). The LC_{50} values of compounds **30** and **31** against *C. elegans* were 0.0733 and 0.0109 mmol/L, respectively, which was better than that of the positive control fosthiazate (0.2798 mmol/L). Meanwhile, compound **30** showed 68.89% lethality against *Spodoptera litura* (*S. litura*), and compound **31** had 36.11% and 34.33% lethality against *S. litura* and *Tetranychus cinnabarinus* (*T. cinnabarinus*) respectively. Despite this, compounds **30** and **31** did not exhibit the same level of activity as tralopyril. This could be due to their inability to fully penetrate the insect epidermis or the mitochondrial membrane after penetrating the epidermis, leading to a reduction in their insecticidal and acaricidal effectiveness. The ability of the compound to enter the organism and successfully break down into the active form of tralopyril is key. While certain larger groups may not be ideal for entering the insect's body, reports suggest that plant amino acids and sugar transport molecules could team up with pesticide molecules to boost their movement in the phloem [43,44]. Chen and Li introduced glucose [45] and amino acids [46] into 1-N to improve the phloem fluidity of drugs. Despite not being as potent in its direct insect-killing abilities as chlorfenapyr, this compound can still be applied through the roots, transported in the phloem, and released upon consumption by insects, ultimately achieving insecticidal effects. Its excellent systemic insecticidal activity enables it to maintain its effectiveness against insects concealed in parts of the plant that are not exposed. Compound **32** (Fig. 2) demonstrated total lethality against *Plutella xylostella* (*P. xylostella*) at 4 mmol/L. Compound **33** (Fig. 2) also displayed strong insecticidal activity, with an LC_{50} of 0.2397 mmol/L. In addition, Wang *et al.* [47] also described an *N*-oxalate derivative. At 20 mg/L, compounds **34–35** (Fig. 2) were effective in completely eliminating pairs of *S. eridania* larvae. Researchers Zhao *et al.* created a selection of *N*-ester tralopyril derivatives by combining reactive groups that have been found. Compound **36** (Fig. 2) (LC_{50} = 0.43 mg/L) showed higher acaricidal activity against *T. urticae* than chlorfenapyr (LC_{50} = 1.14 mg/L). At the same time, compound **36** (LC_{50} = 1.88 mg/L) showed almost the same activity as chlorfenapyr (LC_{50} = 1.82 mg/L) against *P. xylostella* [48]. Meanwhile, when oxalyl groups were added to N [49], compound **37** (Fig. 2) demonstrated impressive insecticidal activity similar to chlorfenapyr; and had a 100% efficiency in insecticidal *M. separata* at 5 mg/L. The structure-activity relationship showed that aromatic substituted compounds had lower insecticidal activity against *M. separata* than saturated short alkyl-substituted compounds. In addition, 2–chloro-5-thiazolyl is a substituent that produces good biological activity [50]. Xu *et al.* [51] obtained a derivative of tralopyril by exchanging the NH of pyrrole with 2–chloro-5-thiazolyl, labeled as compound **38** (Fig. 2). Compound **38** displayed excellent insecticidal activity against *Laphygma exigua (L. exigua)*, *P. xylostella*, and *Chilo suppressalis*, with superior control outcomes compared to chlorfenapyr and chlorantraniliprole. Sun *et al.* [52] reported the incorporation of acetyl groups into the amine of tralopyril, generating compound **39** (Fig. 2), which had excellent preventive effects on *L. exigua*, *P. xylostella*, and apple aphid. There is also a particular type of *N*-ester arylpyrrole derivative, with acetyl groups, that has been shown to possess good insecticidal activity against *P. xylostella*, *S. litura*, *M. separata*, and *T. cinnabarinus*. Notably, compound **40** (Fig. 2) has been reported to be especially effective. Introducing different substituents onto the N atom of tralopyril may reduce its toxicity to plants and mammals, while also altering the insecticidal spectrum compared to the parent compound. Incorporating substituents into the N not only maintains the insecticidal effectiveness of tralopyril, but also widens its potential for disease and pest control. Furthermore, substituting the N of the pyrrole may inhibit the degradation of the active ingredient, resulting in reduced insecticidal activity, however, these groups could enhance the systemic and mobile properties of compounds, such as the amino acid glucose. In terms of modified groups, the substitution of oxoalkyl groups on tralopyril's N, followed by modification, appears to be a promising strategy for obtaining highly active compounds. Alkylation likely increases the lipophilicity of the membrane, thus enhancing its capacity to pass through the membrane layer. The insect's ability to remove the N-protecting group, which is affected by the type of N-substituent, is associated with this function. Additionally, introducing established reactive groups into tralopyril produces surprising outcomes.

The main approach to discovering new pyrrole insecticides still involves optimizing and modifying active derivatives. Arylpyrrole, the primary framework of tralopyril derivatives, is sourced from antibiotics and retains the core structure of natural products, indicating their potential environmental friendliness. Consequently, current studies are concentrated on preserving the fundamental phenylpyrrole skeleton while making adjustments to either the pyrrole or benzene ring. Wang *et al.* [53] were puzzled to find that chlorfenapyr is less structurally similar to the insecticidal dioxapyrrolomycin and more similar to the antibacterial pyrrolomycin E (**11**) (Fig. 1). Despite this, compound **11** does not demonstrate effective insecticidal properties. To explore the structure-activity relationship, the researchers maintained the pyrrole ring and introduced a substituted benzyl or benzoyl group at the 2-position of the pyrrole ring to create a series of compounds **41a-41c** and **42a-42c** (Fig. S1 in Supporting information). Addition-

ally, benzoyl groups were introduced to form compounds **43** and **44** (Fig. S1). Subsequent substitution [54] of H between the two rings with an alkoxy group gave compounds **41d-41h** and **42d-42f** (Fig. S1). They all have good insecticidal activity (more details for structure-activity relationship analysis of compounds (Section S1 in Supporting information). Furthermore, Sun *et al.* [55] maintained the chlorfenapyr structure and added heterocyclic groups to the pyrrole 4-position in order to replace Br, such as thiazolidines and imidazolidines. It was discovered that compounds **45a** and **45b** (Fig. S1) exhibited a higher mortality rate in *L. exigua* and *P. xylostella* compared to chlorfenapyr. Additionally, compounds **45c** and **45d** showed superior insecticidal effects on apple yellow spiders and tobacco planthoppers when compared to chlorfenapyr. Surprisingly Mao *et al.* [56] connected two molecules of tralopyril with a bridging ring to make compound **46** (Fig. S1). At 0.5 mg/L, compound **46** showed 100% insecticidal activity against *M. separata* and mosquito, and its insecticidal activity against *T. cinnabarinus* was similar to that of chlorfenapyr. Although the parent compounds' activity was not impacted by the addition of an aryl oxoxydiazide to the N atom of the diarylhydrazine molecular structure, certain physical properties of the compound were changed. In addition, Li [57] transformed trifluoromethyl into an ester in tralopyril. Unlike compound **45** which alters the 4-position of tralopyril, compound **47** alters it at the 5-position and this alteration can make a difference in their insecticidal spectrum. Compound **47** (Fig. S1) displayed 100% insecticidal activity against *M. separata* when tested at 100 mg/L. Xu *et al.* [58] also found that imines at the 5-position of the pyrrole ring resulted in a 100% lethal rate for compounds **48a-48b** (Fig. S1) against *Culex pipiens* at 10 mg/L. Additionally, compounds **48c-48d** (Fig. S1) showed good lethality against *Aphis craccivura*, and compound **48e** (Fig. S1) displayed high activity against *P. xylostella*. The above literature reports have found that electron-withdrawing groups at the pyrrole 5-position are all effective, whether it is the commonly used -CF_3 or the modified -COOR, -C=NHR. This may indicate that an electron-withdrawing group at the pyrrole 5-position is necessary for insecticidal activity.

Furthermore, a variety of phenylpyrrole analogs display exceptional insecticidal effectiveness. David Chou [59] discovered amino-substituted phenylpyrrole derivatives compound **49** (Fig. S1), which were found to be effective in controlling *H. virescens*. Interestingly, Antar also came across a series of phenylpyrrole compounds with the benzene ring positioned at the 2-position of the pyrrole instead of the usual 1-position [60]. Compound **50** (Fig. S1) displayed potent insecticidal action against *Spodoptera littoralis* (*S. littoralis*), with LC_{50} values of 0.1306 mg/L, respectively. Compound **50** had similar efficacy to the commercially available dimilin drug in controlling *S. littoralis*. Also at the 2-position of pyrrole, in 2020, Abe discovered [61] that heterocyclic substituted pyrrole compound **51** (Fig. S1) had a 100% success rate in controlling *Laodelphax striatella*, *P. xylostella*, and *Myzus persicae*(*M. persicae*) at 500 mg/L. Additionally, this compound is decomposable in the environment. Compounds **52a-52b** (Fig. S1) are simple structures with excellent insecticidal activity, and they are modified from the lead compounds obtained from plant extracts [62]. Noteworthy, two of the synthetic product compounds **52a-52b** have significant insecticidal activity. The acute LC_{50} values for third-instar nymphs of *Oncopeltus fasciatus (O. fasciatus)* exposed to these products by the contact method were 5.26 and 5.07 mg/L, respectively. Although the two compounds have similar LC_{50} values, compound **52a** produced 100% mortality at 7.5 mg/L, whereas compound **52b** showed 73.3% toxicity at the same dose. It appears that when methylation occurs between the two carbonyl groups, there is a notable reduction in the slope of the dose-response curve. Similarly, in 2020, Hu *et al.* [63] discovered a group of pyrrole-2-carboxyl derivatives from the endophytic *Streptomyces* sp. of *Stemona japonica* (Blume) Miq. Compound **53** (Fig. S1) had a 74.99% inhibitory effect on *Aphis gossypii* at 500 mg/L after 3 days, and a 76.92% inhibitory activity against *T. urticae* at 800 mg/L. In 2021, Yang and colleagues discovered a group of bis indole pyrrole compounds from a deep-sea actinomycete *Streptomyces sp*. [64] These compounds showed promising effects on the growth rate and body size of *M. separata*, *Ostrinia furnacalis*, and *Spodoptera frugiperda* (*S. frugiperda*) at 2.5 mmol/L. When the concentration of compound **54** (Fig. S1) was raised to 10 mmol/L, it effectively controlled these insects by inhibiting insect chitinase. Although their activity was moderate, these natural compounds could provide novel modes of action and are eco-friendly, in line with current trends. Therefore, it is necessary to conduct additional research and make adjustments to these compounds.

Phenylpyrrole has been recognized as a potential precursor for improving molecular structures in drug development. Additionally, research has been directed towards altering already established pharmaceuticals to boost their potency. One study by Li *et al.* [65,66] explored replacing pyrazole with pyrrole in chlorantraniliprole, a compound with insecticidal properties. Several derivatives of chlorantraniliprole were synthesized, with compounds **55a-55d** (Fig. 3A) showing good insecticidal activity against *M. separata*. The presence of Cl and Br substituents on the pyrrole ring, along with different R1 substitutions, contributed to the activity of these compounds, with LC_{50} values ranging from 0.47 mg/L to 3.5 mg/L. Unsubstituted compound **55e** (Fig. 3A) exhibited the highest activity with an LC_{50} of 0.21 mg/L. However, both the modified compounds and chlorantraniliprole were found to be more potent than the unsubstituted compound. The compounds **55a-55d** showed better insecticidal activity than the unsubstituted compound **55e** against *P. xylostella*, and surprisingly even at 0.00001 mg/L, compound **55a** still showed 50% insecticidal activity. Subsequently, the group replaced oxygen atoms with sulfur atoms [67], which resulted in compounds **55f-55h** (Fig. 3A) displaying good activity against both *P. xylostella* and *M. separata*. When R_2 was CH_2CF_2, the control effect on *P. xylostella* was 90% better than that of chlorantraniliprole 65% at 0.00001 mg/L, indicating a significant improvement in insecticidal activity. The structure-activity relationship indicated that incorporating halogens onto the pyrrole ring boosts efficacy against *P. xylostella*, but excessive substitution can diminish insecticidal activity against *M. separata*. Furthermore, compound **55h** showed outstanding insecticidal activity, possibly due to the fluorine effect. The insecticidal potency of compound **55f** surpassed that of compound **55e**, indicating that thioamides in the aliphatic amide segment may be more advantageous in enhancing larvicidal activity.

2.2. Pyrrolidine

There are similar modifications in isoxazoline insecticides which work by inhibiting the influx of chloride ions and interfering with γ-aminobutyric acid (GABA) transmembrane signaling, leading to uncontrollable nerve excitability and death in insects. Researchers have discovered that by substituting the isoxazoline ring with pyrrolidine, the insecticidal activity can be improved. Derivatives containing amide groups linked to the benzene ring of pyrrolidine exhibit excellent internal absorption, offering protection not just to the seeds but also to the resulting plants. Compounds **56** and **57** (Fig. 3B) [68] demonstrate impressive internal absorption, with an insecticidal rate of more than 98% against *T. urticae* at 500 mg/L and 100% mortality rate against the third instar of *S. litura* at 100 mg/L. After further investigation, compound **58** (Fig. 3B) [69] exhibits superior insecticidal activity against *T. urticae* and *S. litura* at 100 mg/L. However, these changes are limited to the benzene ring and the substituted amide portion, and for connecting the amide C atom. Compound **59** (*S* configuration) (Fig. 3B) [70] has a chiral center and shows 100% insecticidal activ-

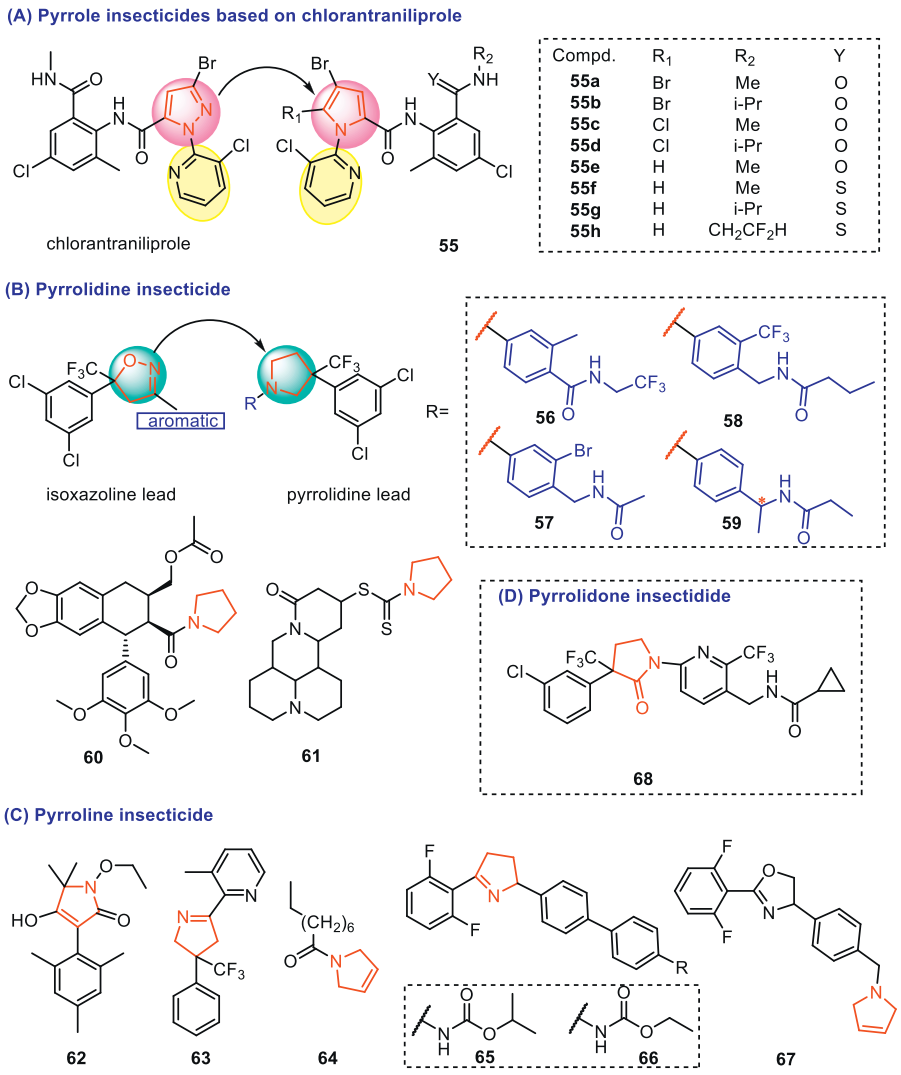

Fig. 3. Pyrrole and its analogs with insecticidal activity.

ity against *T. urticae* and *S. litura* at 20 mg/L and 100% insecticidal activity against *T. urticae* and *S. litura* at 4 mg/L. The activity has been enhanced in comparison to compounds **56**–**58**, with chirality possibly being a significant factor. The presence of an amide group in the para position of the benzene ring directly linked to the pyrrolidine is crucial for maintaining the derivative's activity. The introduction of pyrrole or pyrrole analogs to modify different commercial agents has led to the discovery of compounds with activity comparable to that of the parent compounds. Although they did not succeed in finding new commercial agents, these modifications are undeniably beneficial for the work of future researchers. Studies on the insecticidal activities of natural compounds have been reported, such as toosendanin, a commercial botanical insecticide isolated from *Melia azedarach* [71,72]. In 2014, Wang [73] showed that by adding a pyrrole ring to toosendanin, compound **60** (Fig. 3B) exhibited higher insecticidal activity against *M. separata* compared to toosendanin. Matrine, a quinoline alkaloid, is extracted from the dried root, fruit, and other components of the plant *Sophora flavescens*. Due to its wide range of biological functions, it serves as a valuable asset in pharmacy, agronomy, and numerous other sectors. As a biological pesticide with a lactam structure, matrine has been recommended as a biological pesticide for controlling *S. frugiperda*. However, its effectiveness is limited by low activity, slow efficacy, and poor bioavailability. Altering the configuration of organic substances is a popular approach in creating novel pesticides [74]. It was shown that the introduction of pyrrolidine into matrine, compound **61** (Fig. 3B) significantly enhanced cytotoxicity and increased insecticidal activity against *S. frugiperda* [75]. The bonding of the pyrrole N with a carbonyl group to form an amide group appears to be crucial in the function of pyrrolidine.

2.3. Pyrroline

In 2014, Mitsuru [76] conducted a study regarding the structure of *N*-oxydihydropyrrole, which only reported derivatives with a 1,3-diketone moiety. Compound **62** (Fig. 3C) showed efficacy against *M. persicae* by providing complete control at 0.1 mg/L, without causing any significant phytotoxicity. The trifluoromethyl functional group plays a crucial role in the creation of various pharmaceutical and pesticide molecules by altering their polarity, lipophilicity, and metabolic stability effectively [77,78]. In 2016, Fu [79] combined trifluoromethyl with pyrrole compounds, resulting in a 100% lethality rate in the inhibitory activity test against *P. xylostella*. Compound **63** (Fig. 3C) has the potential to be developed into agricultural insecticides. Similarly, a number of analogs of natural products have been reported. In 2000, Angel [80] altered the active compound derived from *Penicillum brevicompatum* to pro-

duce compound **64** (Fig. 3C) with a 3-pyrroline ring, and it revealed noteworthy insecticidal action against third-instar nymphs of *O. fasciatus* (complete mortality at 7.5 mg/L). In 2003, Seitz described novel pyrroline to control pests. Compounds **65** and **66** (Fig. 3C) [81] showed 100% insecticidal activity at 100 mg/L against *H. virescens*, *P. xylostella* and *L. exigua*. Additionally, Chen showed oxazoline derivatives with a range of *N*-pyrroline substituents at the para benzyl site [82]. Compound **67** (Fig. 3C) exhibited 100% insecticidal activity at 100 mg/L against *T. cinnabarinus*. There have been relatively few insecticidal studies on pyrroline, but there is no shortage of compounds with excellent insecticidal activity. Moving forward, further research could be carried out on pyrroline derivatives.

2.4. Pyrrolidone

In the modification of isoxazolidine precursor, the introduction of pyrrolidone also showed good insecticidal activity. Compound **68** (Fig. 3D) demonstrated 100% insecticidal activity at 20 mg/L against *S. litura* [83].

3. Herbicidal activity

3.1. Pyrrole

Numerous studies have explored the herbicidal properties of pyrrole. For instance, in 2012, Li [84] conducted a study on alkyl analogues of the insecticide chlorfenapyr, with compound **69** (Fig. 4A) showing a significant inhibitory effect on pigweed. At 375 g/ha, it had a 100% inhibitory effect, and even at 750 g/ha, it still had more than 90% inhibitory effect on *B. campestris*. In 2008, Xue [85] employed the active splicing technique to create compounds with pyrrole triazole rings. Compound **70** (Fig. 4A) was found to have an inhibitory rate of over 90% on monocotyledonous and dicotyledonous plant roots (*E. crusgalli* and *B. campestris*) at 10 mg/L. There is also a class of benzoylpyrrole that have been reported to have herbicidal activity, such as 2-benzoylpyrrole compound **71** (Fig. 4A) at 3.57 kg/ha with over 82% herbicidal activity against wild oats and watercress [86]. Further work was carried out to switch the benzoyl group to the 3-position, resulting in compound **72** (Fig. 4A) which showed the same activity with a 96% inhibition rate against wild oats and watercress at 3.57 kg/ha [87]. Arylpyrroles have been extensively studied not only for their insecticidal activity but also for their herbicidal activity. For example, in 2004, Giovanni [88] discovered a new type of photoactivated and membrane-disrupting herbicide, 3-arylpyrrole. Compound **73** (Fig. 4A) can lead to the formation of ethane and a decrease in chlorophyll levels, thus controlling weeds in a similar manner to protoporphyrinogen oxidase (PPO) inhibitors. Additionally, this product has good tolerance in wheat and can control up to 80% of various broadleaf weeds (such as *A. retroflexus*, *pomoea purpurea*, *Solanum nigrum*) at low application rates. When applied at 50 g/ha after sprouting, the product can provide excellent control of broadleaf weeds. In 2000, Meazza [89] discovered compounds **74** and **75** (Fig. 4A), which are phenylpyrrole compounds with impressive herbicidal activity on many weeds. Their low phytotoxicity towards many crops renders them suitable candidates for selective herbicide applications. Laporta [90] elucidates that certain phenyl pyrrole compounds exhibit herbicidal activities against weeds in crop cultivation. These compounds demonstrate efficacy in controlling both monocotyledonous and dicotyledonous weed species at pre- and post-emergence stages, while exhibiting low phytotoxicity towards cultivated crops. Compound **76** (Fig. 4A), when used at a rate of 50 g/ha, has demonstrated more than 90% post-seeding herbicidal activity both before and after emergence. According to the structure-activity relationship analysis, the key factor in herbicidal activity lies in the incorporation of functional groups on the nitrogen atom of the pyrrole ring. *N*-Alkylated derivatives are found to be more effective, with *N*-methyl and *N*-ethyl providing the best results. However, larger or branched alkyl groups do not seem to be very effective. When it comes to the substituents on the 2- and 4-positions of the benzene ring, the herbicidal activity is similar to that of other proton inhibiting herbicides. A halogen group is needed at the 2-position, with fluorine being the most effective. At the 4-position, a small, lipophilic, electronegative group is required, with bromine and chlorine being the best choices. Substituting the pyrrole N with methyl may be necessary for herbicidal activity. The environmental friendliness of phenylpyrrole is also seen in its herbicidal activity, which should be further studied.

3.2. Pyrrolidine

Pyrrolidine compounds may also demonstrate effective herbicidal properties. Cisanilide (Fig. 4B) is a pyrrolidine herbicide commonly used in agriculture that blocks the Hill reaction in spinach chloroplasts [91]. Moreover, the pyrrolidine structure is found in new natural herbicides as well. Huang *et al.* mention compound **77** (Fig. 4B) sourced from dry long pepper (*Piper longum* L.) fruits, showing effective herbicidal properties against *E. crusgalli*. In addition, compound **78** (Fig. 4B) was synthesized simultaneously and also demonstrated potent herbicidal activity [92].

3.3. Pyrroline

Additionally, pyrroline derivatives display outstanding herbicidal activities. For instance, the thioalkyl pyrrolamide derivative **79** (Fig. 4C) was proven to be 100% effective in suppressing ryegrass, *Agrostis tenuis*, *Lolium perenne*, and *Setaria viridis* at 1900 g/ha [93].

3.4. Pyrrolidone

Moreover, there is a substantial number of pyrrolidone compounds that have demonstrated herbicidal activity. Here is a type of 2-pyrrolidone that has been extensively studied for its herbicidal activity. Fluorochloridone (Fig. 4D) is a selective pyrrolidone herbicide that was developed by the former Stofu Petrochemical Company in the United States during the 1970s. It has been observed that fluorochloridone induces cell apoptosis through the regulation of mitochondrial dysfunction and oxidative stress [94]. However, not much research has been done recently on its structure and bioactivity, mostly examining it as a composition. Additionally, Seiji has identified [95] a new pyrrolidone compound that has a good effect on *E. crusgalli*. The experiment revealed that compound **81** (Fig. 4D) has higher herbicidal activity than compound **80** (Fig. 4D), which has a methoxycarbonyl group that can be broken down into carboxyl groups by esterase in plants and then decarboxylated to its active form compound **81**. The addition of esters to the pyrrolidone structure is important for herbicidal activity because it can improve selectivity and decrease toxicity to rice. PPO herbicides are seen as potential frontrunners for the evolution of new herbicides due to their advantageous features like environmental friendliness, low toxicity, and resistance [96,97]. PPO can catalyze the conversion of protoporphyrinogen IX (Protogen IX), which is a key enzyme in chlorophyll synthesis [98]. Protogen IX is a tetrapyrrole compound [99]. It has been reported that the higher the molecular similarity between a PPO inhibitor and protogen IX, the stronger their enzyme inhibition activity [100]. In 2020, Zhao [101] created pyrrolidone derivatives with phenoxy pyridine, and compound **82** (Fig. 4D) had an IC_{50} of 0.041 mg/L, which was more effective in inhibiting PPO than the Oxyfluorfen's IC_{50} of 0.043 mg/L. Compound **82** can reduce the chlorophyll a and b content in *Abutilon theophrastis* to 0.306 mg/L

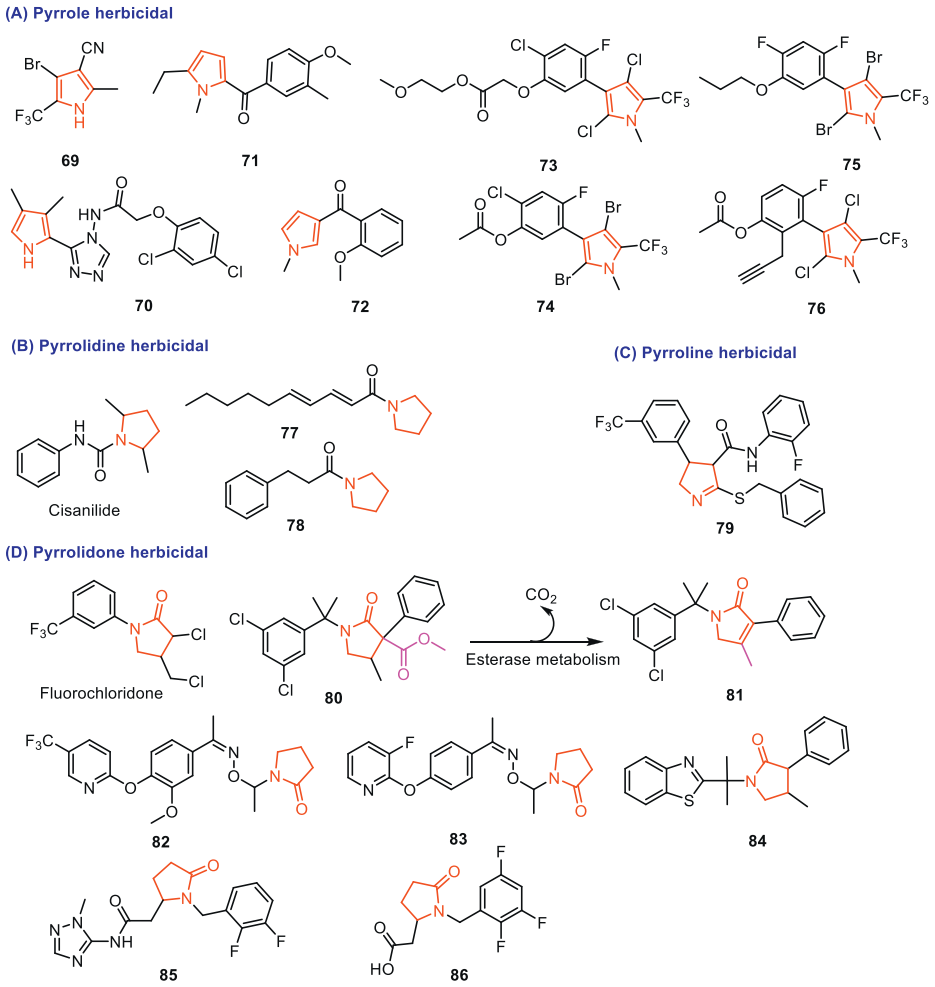

Fig. 4. Pyrrole and its analogs with herbicidal activity.

and 0.217 mg/L, respectively. Furthermore, compound **82** acts more tightly on the active site than oxyfluorfen. Subsequently, they also discovered [102] that compound **83** (Fig. 4D) had a stronger PPO enzyme inhibitory activity than the commercially available Oxyfluorfen, with an IC_{50} of 0.0262 mg/L compared to 0.0426 mg/L. Moreover, the greenhouse herbicidal activity test showed that compound **83** maintained effective broad-spectrum herbicidal activity even at a dosage of 37.5 g a.i./ha. The above literature summarizes that the introduction of pyrrolidone can indeed increase the herbicidal activity of compounds. In 2000, Masahiko [103] synthesized a new pyrrolidone compound **84** (Fig. 4D) called MI-2826 which showed high activity against *Lindernia pyxidaria*, *Elatine triandra*, and *Rotala indica*, especially *E. crusgalli*. This compound possesses long-lasting herbicidal activity against *E. crusgalli* after application. In 2022, Arve [104] identified a group of pyrrolidone compounds containing amides or acids that were highly effective in controlling invasive plants even when applied at low rates. Both compounds **85–86** (Fig. 4D) showed more than 80% effectiveness against *Alopecurus myosuroides*, *Avena fatua*, *D. sanguinalis.*, *E. crusgalli*, and *Lolium rigidum* at 320 g/ha both pre- and post-emergence.

In addition, tenuazonic acid (TeA) (Fig. S2 in Supporting information) is a 2,4-pyrrolidinedione derivative that was first extracted from the fermentation broth of the fungus *Alternaria alternata* [105]. It has been found to be highly effective in inhibiting the growth of both monocotyledonous and dicotyledonous weed seedlings. Studies have shown that it hinders photosynthesis by hindering the movement of PSII electrons from the plastid quinone QA to QB [106,107]. The results of competitive displacement with [^{14}C] atrazine combined with the JIP test, suggest that TeA is a new type of PSII inhibitor [108]. However, mandatory testing of TeA as an unavoidable contaminant in food and feed due to health concerns [109], as well as the fact that TeA easily changes conformation and is unsuitable for industrial application, have hindered the commercial development of TeA as a herbicide. Because of its exceptional herbicidal properties, TeA has attracted significant attention from pesticide developers who are working on creating new microbial herbicides. Through altering the substituents at different positions, researchers have been able to modify the derivatives structure, leading to different degrees of herbicidal effectiveness. The primary focus for modification lies on the acyl group at the 3-position and the alkyl group at the 5-position of the pyrrolidone ring. In 2005, Qiang discovered that the addition of a saturated haloalkyl compound **87** (Fig. S2) [110] and a sulfur-containing group compound **88** (Fig. S2) [111] at the 5-position of TeA had an effect on its herbicidal activity. The herbicidal activity of compound **88** was found to be higher when a chlorinated alkyl group was present. Moreover, compound **88**, which featured a mercaptomethyl substitution, displayed significant effectiveness in controlling most weeds at 1 mg/L. At the 5-position of pyrrolidine, Han in 2012 [112] added alkyl and substituted benzyl groups, resulting in compounds **89** and **90** (Fig. S2) with good herbicidal activity against *Echinochloa crusgalli* (*E. crusgalli*). The EC_{50} values for these compounds were 94.4 mg/L and 72.7 mg/L respectively, with inhibitory rates on *E. crusgalli*, stems of 62.6% and 66.9%, both

higher than the 51.0% of TeA. In terms of 5-position derivatization, the hydrophobic group at the 5-position plays a crucial role, and halogenated alkyl groups are excellent choices.

Apart from adjusting TeA's 5-position, there have also been modifications made at the 3-position. For example, in 2005, Zhu [113] modified the pyrrolidone by introducing a substituted benzene ring into its 3-position. Compound **91** (Fig. S2) was found to be more effective in inhibiting the growth of *Brassica campestris* (*B. campestris*) than the positive control drug sulcotrione, and it also showed good herbicidal activity against monocotyledonous plants such as *E. crusgalli* and *Digitaria sanguinalis* (*D. sanguinalis*). The structure-activity relationship indicates that substituents on the benzene ring that donate electrons are more effective in inhibiting growth. By replacing the benzyl group on N with isopropyl, the resulting herbicide showed a 100-fold increase in activity against *E. crusgalli* compared to compound **91**. The substituents on the benzene ring at the 3-position were altered. Electron-donating substituents showed better activity, which may be attributed to their ability to facilitate the formation of enol isomers, thus increasing the likelihood of the compound binding to the 4-hydroxyphenylpyruvate dioxygenase (HPPD) center. Additionally, these compounds exhibited growth inhibition and bleaching properties, with the benzene ring effectively preserving this conjugated system. Compounds **92a-92b** (Fig. S2) have superior herbicidal activity compared to sulcotrione and completely eradicate monocotyledonous plants such as *E. crusgalli* and *D. sanguinalis*. Compound **92b** has a selectivity of 187.5 g/ha for corn and soybean before sprouting, and a control effect of 93% [113,114]. To further explore the variety of this compound, Zhu replaced phenyls with substituted heterocycles [115]. Compounds **92c-92d** (Fig. S2) were synthesized, leading to a notable enhancement in the inhibition rate of rapeseed; however, they did not show a significant impact on the growth inhibition of *E. crusgalli*. This shows that the introduction of larger groups is advantageous for suppressing the growth of dicotyledonous plants, but does not yield the same results for inhibiting monocotyledonous plants. When substituted with a thiophene ring **(92c**) and a pyridine ring (**92d**) (Fig. S2), it showed good inhibition activity against *E. crusgalli* at 10 mg/L, with 52% and 60%, respectively. Subsequently employing the principle of biological equivalence, the indole ring was introduced into the 3-position of pyrrolidone [116]. At 100 mg/L, compound **93** (Fig. S2) exhibited a certain degree of herbicidal activity against *E. crusgalli* and *B. campestris*. Subsequently, by replacing the 3-position with cyclopropane, compound **94** (Fig. S2) showed the most effective inhibitory rate of 89% against *E. crusgalli* at 100 mg/L, and it also showed good activity against *B. campestris*. In 2012, Liu introduced cyano, sulfonyl, and amino groups to the 3-position of the 2,4-pyrrolidinedione ring. The cyano compound **95** (Fig. S2) and the sulfonyl compound **96** (Fig. S2) were synthesized using the Dieckmann reaction, while the amino compound **97** (Fig. S2) was formed from 3-carboxylate derivatives with the aid of microwave technology. Although no herbicidal activity was observed, compound **97** had a bleaching effect on weed leaves, suggesting a possible binding with HPPD. Compound **95** exhibited some insecticidal activity. Following this, a hydrazine group was introduced at the 3-position [117]. In comparison to TeA, the 3-hydrazido compounds **98a-98e** showed relatively better herbicidal activities. In particular, *N*-arylcarbonyl compounds **98b-98c** (Fig. S2) showed a 55% inhibition rate on *Amaranthus retroflexus* (*A. retroflexus*) weed control, which was greater than that of the hydrophilic *N*-acetyl compound **98a** (Fig. S2), the *N*–*tert*-butoxycarbonyl compound **98e** (Fig. S2), and the ethoxycarbonyl compound **98d** (Fig. S2). The 3-hydrazono compounds **99a-99e** (Fig. S2), based on 3-hydrazine, showed good herbicidal activity against dicotyledonous plants such as *B. campestris* and *A. retroflexus*. However, the structure-activity relationship of these compounds was the opposite of that of compounds **98a-98e**. The activity of compounds **99b-99c**, which have aromatic carbonyl groups on nitrogen, was weaker than that of the *N*-acetyl compound **99a** and the *N*-alkoxycarbonyl compounds **99d-99e** [118]. In 2009, Zhu introduced oxime ether structure for TeA, where they substituted the 1-position with a phenyl group. Compound **100** (Fig. S2) was found to be effective in controlling the growth of *B. campestris* and *E. crusgalli*. At 100 mg/L, compound **100** showed an inhibition rate of 66.2% against *B. campestris* [119]. Surprisingly, compound **101** (Fig. S2) features an oxime ether structure at the 3-position and a cycloalkyl group at the 1-position. Despite this difference, it displayed inhibitory rates exceeding 70% against *B. campestris* at the same concentration. In both cases, the inhibitory rates against *B. campestris* were found to be over 80% [120]. The change in substituents improved the derivatives activity. Simultaneously, Wang *et al.* [121] added amines to the 3-position of 2,4-pyrrolidinedione. At 100 mg/L, compound **102** (Fig. S2) was able to inhibit the growth of *E. crusgalli* and *B. campestris* by 94.4% and 67.4%, respectively. In 2011, Si *et al.* [122] uncovered a novel semicarbazide structural unit at the 3-position of 2,4-pyrrolidinedione. Compound **103** (Fig. S2) showed an inhibitory activity of 86% against *B. campestris*. The group attached at the 3-position is typically the one capable of preserving the pyrrolidone conjugate system. Examples include the ketone structure with the alkenyl group attached and the enol group connected to the carbonyl group, both of which contribute to the continuation of the pyrrolidone conjugate structure. The presence of an electron-withdrawing group is crucial in this process.

While there is an abundance of research on 3- or 5-substituted TeA, there is comparatively less research on compounds derived from the 1- and 4-position. For instance, in 2014, Liu [123] presented an amino group at the 4-position of pyrrolidone. Compound **104** (Fig. S2) was found to have good herbicidal activity against *Arabidopsis thaliana*. Additionally, 4-position derivatives containing an ether [124] such as compounds **105** and **106** (Fig. S2), have been studied. Compound **105** which contains a methoxyethyl moiety, exhibited a 53.6% inhibitory rate on the roots of *E. crusgalli*. On the other hand, compound **106,** which contains phenoxy groups, showed the highest inhibitory rate on the roots of *B. campestris* seedlings at 84.0%. The literature reports mentioned earlier highlight the effectiveness of compounds with electron-donating groups at the 1- and 4-positions of pyrrolidone in terms of herbicidal activity. Herbicides that contain a chainlike alkoxy alkyl or substituted phenoxyalkane moiety also exhibit satisfactory herbicidal activity, making them worthy of attention from pesticide researchers.

4. Antifungal activity

4.1. Pyrrole

In the mid-1960s, Arima first identified pyrrolitrin, an arylpyrrole antibiotic, from *Pseudomonas pyrrocinia* [125]. Further experiments conducted *in vivo* and in greenhouse settings confirmed its effectiveness in combating plant pathogens like *Botrytis cinerea* (*B. cinerea*) and *Pyricularia oryzae* (*P. oryzae*). Nevertheless, chemists discovered that its photostability was lacking, prompting them to investigate methods for enhancing its durability while maintaining its effectiveness. Fenpiclonil and fludioxonil (Fig. 5A), two commercial fungicides, have been developed by optimizing and synthesizing their natural structure [126,127]. These compounds are effective against various types of fungi and are safe for mammals and the environment. Phenylpyrroles are the first commercial fungicides that interfere with pathogens through the inhibition of a protein kinase. They bind to protein kinase-III, inhibiting its activity, and preventing the phosphorylation of regulatory proteins. This leads to uncontrolled glycerol production, increased in-

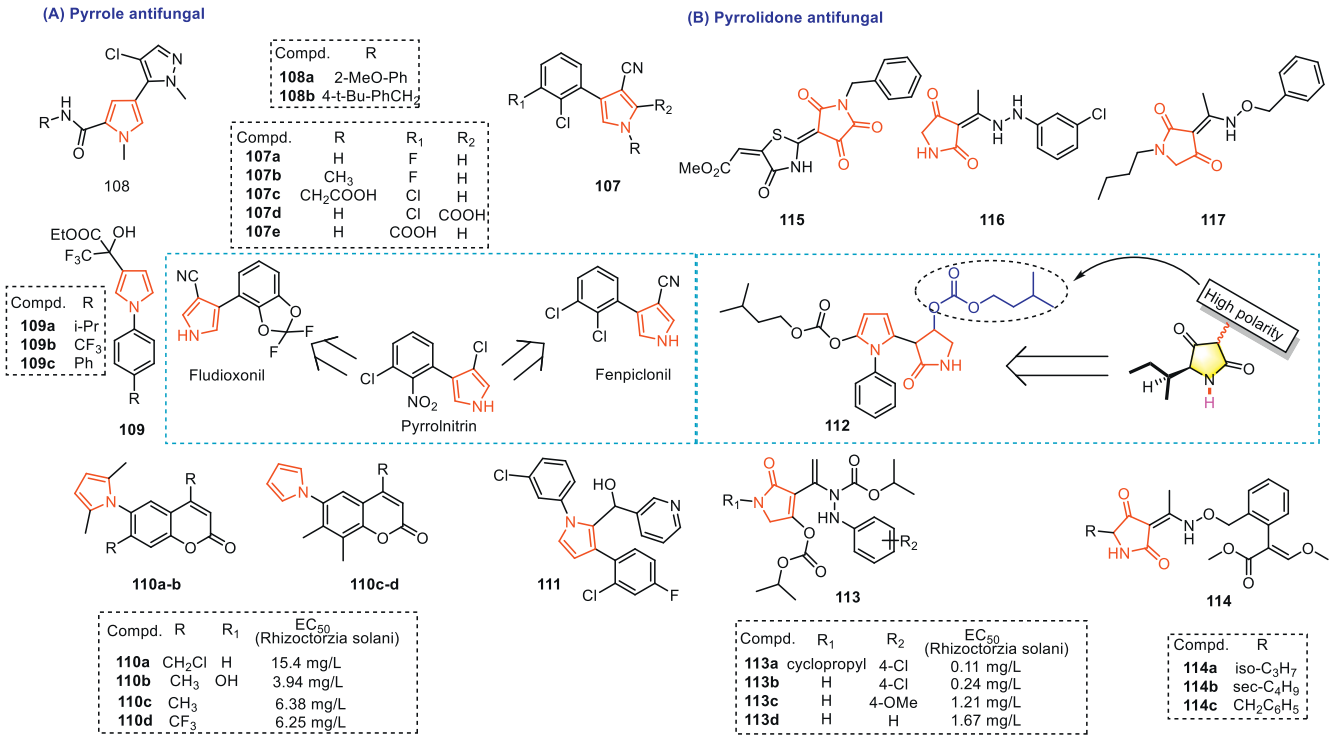

Fig. 5. Pyrrole and pyrrolidone with antifungal activity.

tracellular osmotic pressure, and cell death by swelling [128]. With their impressive non-endothermic characteristics, Fenpiclonil and fludioxonil are being acknowledged for their high efficacy, extensive spectrum of activity, minimal dosage needs, and prolonged duration of action. They have also inspired scientists to study their structure and make numerous modifications. For example, Xu *et al.* [129] added methyl groups to the pyrrole ring of the fungicide fenpiclonil. However, compound **107b** (Fig. 5A) only showed inhibitory activity against *Rhizoctonia solani* (*R. solani*). Then compound **107a** (Fig. 5A) changed the Cl on the benzene ring to F based on fenpiclonil. At 1 mg/L, the inhibitory rates against *P. oryzae* and *Fusarium oxysporum* (*F. oxysporum*) were 65.00% and 83.56% respectively, which were higher than those of fenpiclonil (54.28% and 77.92%). The carboxyl group was then introduced on the pyrrole N of fenpiclonil [130], resulting in compound **107c** (Fig. 5A) exhibiting lower antifungal activity at low concentrations than fenpiclonil. However, compound **107c** exhibits moderate phloem-mobility, in contrast to fenpiclonil. This implies that this derivative is relatively stable, allowing for efficient export from the leaf tissues and long-distance transport throughout the plant. Despite this, compound **107d** (Fig. 5A) showed no antifungal properties, highlighting the significance of the carboxyl group substitution on the pyrrole for its activity. Then, it was shown that compound **107e** (Fig. 5A) with carboxyethyl in NH [131], improves the phloem systemicity at pH 5.0. Additionally, compound **107e** demonstrated increased fungicidal activity in comparison to fenpiclonil. Changing both the group and its position on fenpiclonil could yield diverse results. In 2017, Yao [132] identified some new pyrazole pyrrolamide derivatives. Compounds **108a-108b** (Fig. 5A) showed remarkable fungicidal activity against *Sclerotinia sclerotiorum* and *R. solani*, which was similar to the fungicidal activity of the commercially available succinate dehydrogenase inhibitor (SDHI) thifluzamide. In 2022, An *et al.* [133] reported that a range of 1-phenylpyrrole derivatives not similar to the 4-phenyl pyrrolitrin derivative demonstrated outstanding antifungal effects. Compounds **109a-109c** (Fig. 5A) demonstrated effectiveness against *Citrus anthracnose, F. oxysporum,* and *B. cinerea* at 6.25 mg/L, with an antifungal rate exceeding 80%. The utilization of active compounds to splice with pyrrole is a valuable strategy for studying pyrrole bioactivity. Reports indicate that modifications to osthol's structure can increase its restraining effect on some plant-based fungi [134,135]. For example, Zhang [136] created coumarin derivatives with 7-pyrrole substituents, using osthol as the lead structure. Compound **110a** (Fig. 5A) was more successful in controlling *Cucumber anthrax* and *Alternaria* leaf spot than osthol, with an *R. solani* activity of 15.4 mg/L (EC_{50}), surpassing osthol's 67.2 mg/L (EC_{50}). Based on the initial compound [137], compounds **110b-110d** (Fig. 5A) were found to have a substantial inhibitory effect against *R. solani* at 50.0 mg/L, with inhibition rates of 78%, 75%, and 77% respectively, which surpassed the inhibition rate of osthol (68%). Moreover, compound **110b** was found to be powerful enough to control the mycelial development of both *B. cinerea and Cucumber anthrax*, with inhibition rates of 59% and 53%, respectively, much higher than osthol (47% and 17%, respectively). To further explore the antifungal activity of the synthesized compounds, the EC_{50} values of compounds **110b-110d** against *R. solani* were measured (Fig. 5A), all of which were superior to osthol with an EC_{50} of 9.78 mg/L. The structural optimization of derivatives of 7-pyrroloxycoumarins should be prioritized for the development of more potent antifungal agents. Additionally, exploring the binding of these active structures to pyrrole compounds is crucial for further advancements in this field. In addition, in 2008, Peter declared that compound **111** (Fig. 5A), a phenylpyrrole, had the capacity to inhibit 80% or more of *B. cinerea*, *Mycosphaerella arachidis*, *Septoria tritiei*, and *Fusarium culmorum* at 20 mg/L.

4.2. Pyrrolidone

Tenuazionic acid (TeA), originally known for its herbicidal properties, is now gaining attention for its antifungal activity. Xu *et*

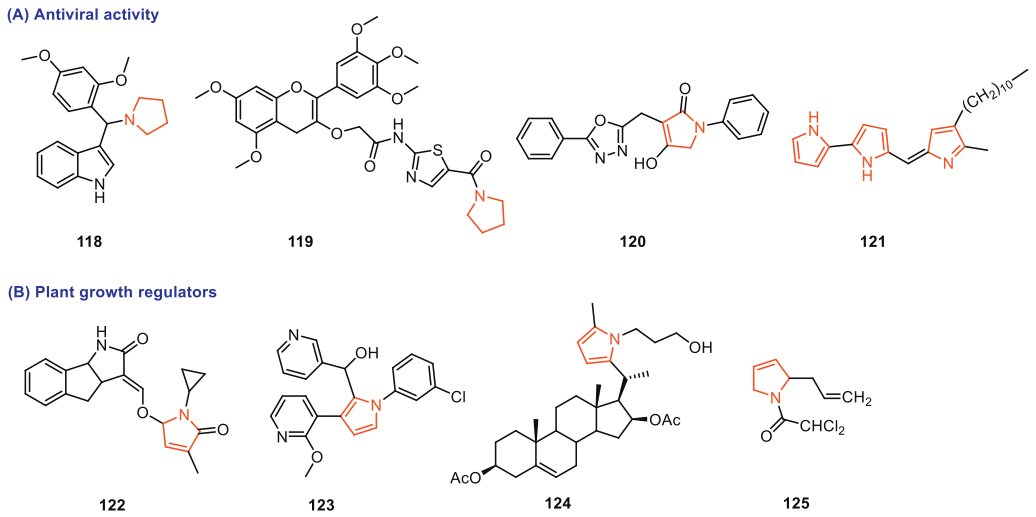

Fig. 6. Pyrrole and its analogs with antiviral activity and plant growth regulators.

al. [138] created a range of TeA derivatives by substituting phenyl pyrrole compound **112** (Fig. 5B) with carbonates. The derivative showed strong inhibitory effects on various plant pathogenic fungi, including *Fusarium graminearum* (*F. graminearum*), *B. cinerea*, and *R. solani* at 100 mg/L. Notably, a significant 82.2% inhibition rate was observed specifically against *B. cinerea*. The compound's antifungal activity could be influenced by the existence of a sizable polar fragment at the 3-position of the pyrrolidone skeleton. In a study by Chen *et al.* [139] in 2020, a carboxyl group-containing phenylhydrazine was introduced at the 3-position of pyrrolidone. Compound **113a** (Fig. 5B) showed comparable *in vivo* control effects to carbendazim against *F. graminearum* and *R. solani*. Compound **113a** with a cyclopropyl at the R_1 demonstrated a better EC_{50} value than compound **113b** (Fig. 5B), which has hydrogen atoms at the R_1 position. Moreover, whether the substituent at the 4-position of the benzene ring is electron-donating, as seen in compound **113c** (Fig. 5B), or electron-withdrawing, as in compound **113b**, the target compound with a substituent (R_2) exhibited superior antifungal activity compared to the unsubstituted compound **113d** (Fig. 5B). The EC_{50} values for these compounds are provided in Fig. 5B. In general, the results emphasize the significance of incorporating a bulky electron-donating group at the 1-position of the pyrrole ring, a substantial electron-withdrawing group at the 4-position of the benzene ring, and a minor alkyl group on the carbonate moiety to enhance the against *R. solani* properties of the compound. In 2014, Lu [140] explored the potential of oxime ether and Schiff base at the 3-position of pyrrolidine, and their derivatives showed better inhibitory activity against plant pathogenic fungi than the naturally occurring TeA. Several compounds exhibited strong inhibitory activity against *R. solani*, with compounds **114a-114c** (Fig. 5B) showing inhibitory rates of 65.2%, 58.5%, and 56.1%, respectively. The biological activity of pyrrolidine was enhanced by adding oxime ether groups at the 3-position of TeA and benzyl groups at the 5-position. Konstantin [141] synthesized compound **115** (Fig. 5B), which displayed high activity against *Alternaria solani* ($EC_{50} = 0.052$ mg/L) and *Phytophthora infestans* ($EC_{50} = 0.087$ mg/L). Compound **116** (Fig. 5B), described by Yang *et al.* [142] demonstrated effective antifungal properties toward various fungi. It was found to be an effective antifungal against *F. graminearum* ($EC_{50} = 0.2702$ mg/L), *B. cinerea* ($EC_{50} = 0.7937$ mg/L), *R. granarium* ($EC_{50} = 0.1613$ mg/L), and *Colletotrichum capsic* ($EC_{50} = 0.6905$ mg/L). Additionally, Zhao [120] found that compound **117** (Fig. 5B) had excellent antifungal activity and higher fungicidal activities than TeA. Compound **117** exhibited antifungal activity against *F. graminearum*, *Rhizoctonia cerealis*, and *Colletotrichum orbiculare* at 100 mg/L, resulting in inhibition rates of 50.5%, 57.8%, and 68.8%, respectively.

5. Antiviral activity and plant growth regulators

There has been a lack of research on pyrrole derivatives in antiviral studies in recent years, with most studies focusing on using pyrroles as substituents, such as adding a pyrrolidine group to the indole alkaloid gramine. Compound **118** (Fig. 6A) demonstrated better anti-TMV activity than ribavirin. It exhibited a 57% inactivation rate, 53% curative rate, and 61% protection rate at 500 mg/L [143]. Similarly, compound **119** (Fig. 6A) introduced a pyrrolidine into myricetin, a flavonol compound extracted from the bark and leaves of myricaceae plants. Compound **119** showed an 86.1% inactivation rate, 83.6% curative rate and 80.3% protection rate at 500 mg/L anti-TMV. It also demonstrated better protective effects anti-TMV compared to ningnanmycin [144]. Another study by Wang *et al.* [145] highlighted the anti-TMV activity of compound **120** (Fig. 6A), a pyrrolidone derivative, with a curative rate of 42.3% at 500 mg/L. Additionally, a tri-pyrrole ring compound **121** (Fig. 6A) extracted from [146] from *Serratia marcescens* 2A2 was found to target TMV effectively, rendering it inactive and reducing its infectivity at 10 mg/L. It showed 99% protection anti-TMV at 10 mg/L. However, pyrrole derivatives have not been extensively researched for their antiviral properties, and their mechanisms of action remain poorly understood. In order to find more antiviral active compounds in the future, mechanistic studies are crucial.

There have been limited studies on pyrrole derivatives as plant growth regulators, but some research has indicated that certain pyrrole compounds can enhance seed germination and promote plant growth. For example, compound **122** (Fig. 6B) has been found to promote the germination of *Orobanche cumana* seeds, with a germination rate of 68% at a concentration of 0.01 mg/L [147]. Surprisingly, the substituted pyrrole-containing compound **123** (Fig. 6B) has been found to possess plant growth regulating properties [148]. At 600 mg/L, the plant height was observed to decrease with the use of compound **123**. Moreover, plants treated with steroidal pyrrole compound **124** (Fig. 6B) exhibited significantly higher root dry biomass. This suggests a positive impact on root growth and offers an advantage to the treated plants [149]. Pyrrole compound **125** (Fig. 6B) has observed a pronounced growth activity(51.4% at the dose of 10 g (t of seeds)$^{-1}$), which is mainly directed on the development of the root system [150].

6. Summary and outlook

Recent studies indicate that pyrrole compounds have a wide range of biological activities, including insecticidal, herbicidal, antifungal, fungicidal, antiviral, and plant growth regulation properties. The research on the efficacy of pyrrole compounds is predominantly focused on natural products. Arylpyrrole and 2,4-pyrrolidinedione are commonly seen as natural product structures of pyrrole. Tralopyril, a phenylpyrrole derivative with potent insecticidal properties derived from dioxapyrromycin, is currently a popular research topic due to its potential for modification based on tralopyril. The literature reports cited above have demonstrated that incorporating functional groups (such as esters, heterocycles, acyls) at the 1-position of tralopyril can preserve its insecticidal activity while potentially enhancing its other biological activities. Furthermore, due to the modification of the parent structure from natural products, its environmental compatibility is also good. Research has shown that introducing electron-withdrawing groups around the pyrrole nucleus is essential for obtaining good insecticidal activity (such as trifluoromethyl, bromine, chloride, ester, sulfonic acid). At the same time, various substituents (such as carboxyl, amino acids, and other macromolecules) on pyrrole or tralopyril may affect the entry of compounds into cells, thereby affecting their overall activity. Whether they can successfully enter the organism and decompose into active compounds may be the key to discovering new commercial drugs. TeA, 2,4-pyrrolidinedione derivatives extracted from *Alternaria alternata* can cause damage to plant leaves and are often used in weed control research. Nevertheless, concerns have been raised about its safety, Modification of N at the 1-position is mostly phenyl and alkyl, with isopropyl being the most prominent, while the electron-withdrawing group at the 3-position may be the key to herbicidal activity. Furthermore, pyrrolidone has been extensively studied for its antifungal properties, with the large polar group on the ring playing a crucial role in its antifungal activity.

The pesticides obtained from and adapted from these natural products showcase various effects, possess a wide range of activity, and are environmentally safe. In the future, the emphasis on exploring and enhancing natural products such as arylpyrrole and pyrrolidone will continue to be a key priority. Additionally, other pyrrole-containing natural structures also have great potential. Although there are many reports on the herbicidal and antifungal activities of pyrrole structures, most of the studies did not continue to explore the mechanism. Therefore, the mechanisms (or targets) of herbicidal and antifungal activities of most pyrrole derivatives are still unclear, which limits to some extent the in-depth optimization of their structures. To delve deeper into the potential mechanisms, targets, and sites of active molecules, one could employ techniques like molecular biology, probes, quantitative proteomics analysis, and micro thermal electrophoresis. These methods could assist in the creation of novel pesticides containing pyrrole compounds.

The focus of research on the biological activity of pyrrole compounds has mainly been on modifying active natural pyrrole compounds. This coincides with the increasing interest in plant-derived pesticides, leading to more research being carried out due to their environmentally friendly characteristics. Therefore, it is a promising approach to continue discovering more natural pyrrole products with potential biological activity. However, its stability and economy should be the main concern. The ability to facilitate factory synthesis and stable application is the key to commercialization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Anjing Liao: Writing – original draft, Visualization, Validation. **Wei Sun:** Validation, Investigation. **Yaming Liu:** Visualization, Validation. **Han Yan:** Visualization, Validation. **Zhi Xia:** Supervision. **Jian Wu:** Writing – review & editing, Supervision, Resources.

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Supplementary materials

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