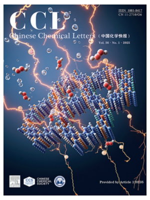
Chinese Chemical Letters 36 (2025) 109855

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet



Research progress on piperidine-containing compounds as agrochemicals

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ARTICLE INFO

Article history:
Received 9 January 2024
Revised 26 March 2024
Accepted 2 April 2024
Available online 3 April 2024

Keywords:
Piperidine
Agrochemicals
Biological activity
Structure-activity relationships
Mechanism of action

ABSTRACT

Piperidine is a crucial pharmacophore and a special scaffold in the realm of drug discovery. Its flexibility increases the molecule's capability to bind to the receptor. The piperidine-containing compounds are distinguished by their remarkable activity, and are increasingly becoming a vital category of pesticides. In this review, the research progress of piperidines in the discovery of pesticides was updated according to their active characteristics. The structure-activity relationships (SARs), and mechanisms of action of piperidine-containing compounds were also discussed. This article is meant to enable readers to quickly understand piperidines, while providing ideas for creating piperidines with novel structures and unique mechanisms of action.

1. Introduction

Piperidine is a heterocyclic structure with a six-membered ring, made up of five methylene groups (-CH_2-) and one amine group (-NH-). It is mainly synthesized through various routes, such as hydrogenation or reduction reactions, intermolecular cyclization, and intramolecular cyclization [1–4]. Piperidine is employed for a variety of purposes, such as a solvent, base, accelerator for rubber vulcanization, and as a component in the production of pharmaceuticals [5–7]. According to FDA approval of drugs on the market, 59.00% of small molecule drugs contain an azacyclic backbone, with the highest percentage being piperidine drugs. Of all the drugs containing piperidine, the largest number of them had substituents present at the 1 and 4 positions on the piperidine [8]. So far, the piperidine fraction has been the main scaffold for drug design as far as possible. Among piperidine-containing drugs, it possesses some unique features: (1) By introducing a piperidine ring to substitute other groups, the interaction of drug molecules with their targets has been improved, as well as their pharmacokinetic properties have been enhanced. For example, in 2020, Takeda reported the discovery of a GPR40 full agonist (SCO-267), which is being utilized in therapeutic studies for diabetes and is currently in phase I of clinical trials [9]. (2) Introducing a piperidine ring improves the metabolic stability of the compound. For example, substituting the piperazine ring of KRCA-0008 with a piperidine ring may result in improved metabolic stability [10]. (3) The piperidine ring increases the water solubility of the drug molecule [11]. (4) Introducing piperidine rings to solve drug resistance problems [12]. The bipiperidine structure was introduced, which enables the drug to enter the lipid bilayer and bind to *P*-glycoprotein, thus solving the problem of drug resistance. (5) Drugs that contain piperidine have the ability to easily cross cell membranes. For example, the analgesic meperidine is able to readily cross the blood-brain barrier. Additionally, Khazanov *et al.* synthesized a piperidine compound that can cross the cell membrane of tumor cells [13]. (6) Piperidine has a strong ability to expand its chemical space, often playing the role of a bridge in drug molecules.

Compounds with a piperidine structure are commonly utilized to manufacture drugs that have a variety of pharmacological effects [14–16]. Piperidines are frequently used in agrochemicals, such as fungicides, insecticides, and herbicides. Piperidines are also often studied for their potential use in pharmaceuticals to treat antitumor activity, cerebrovascular diseases, and the central nervous system [17,18]. Simultaneously, safety assessment is a necessary component of clinical trials and regulatory approvals to ensure that biochemical preparations with piperidine structures are safe and reliable for human use. Agricultural commercial drugs (Fig. 1) with the piperidine group include the fungicides oxathiapiprolin [19,20] and fluoxapiprolin [21], the insecticide spiropidion [22], and the herbicide cypyrafluone [23,24]. Among them, oxathiapiprolin and fluoxapiprolin are two low-toxicity fungicides that have been tested for acute oral, percutaneous, and acute inhalation toxicity in rats [21]. Furthermore, oxathiapiprolin

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https://doi.org/10.1016/j.cclet.2024.109855

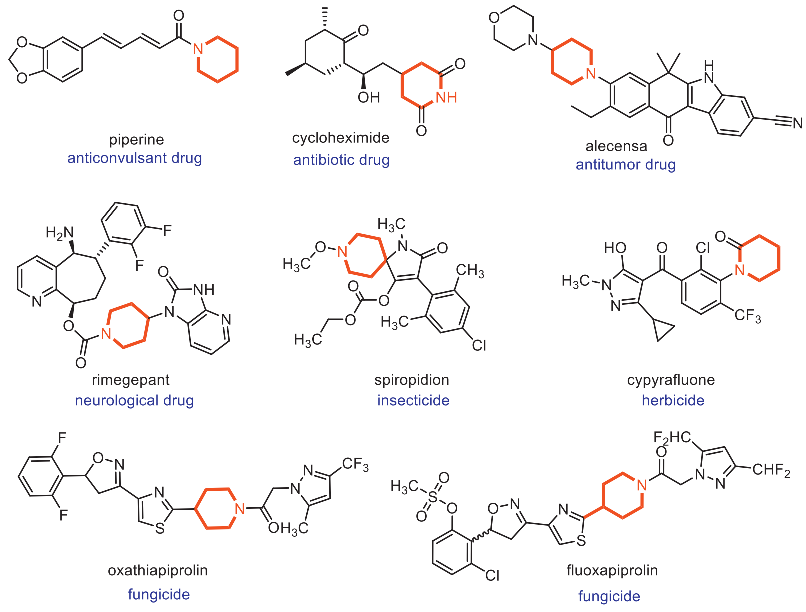


Fig. 1. Structures of piperidine-containing commercial drugs.

has been established to not cause any irritation to the skin, eyes, or respiratory system, it is also not carcinogenic, mutagenic, or toxic to reproductive development [25]. Cypyrafluone is generally considered to have low toxicity, but it can cause temporary damage to enzymes, microorganisms, and earthworms in soil, and chlorella when administered in large amounts. However, these effects are not permanent [26]. Spiropidion has advantageous toxicological and environmental properties, and is not detrimental to pollinating insects and non-target organisms [22]. Furthermore, it has been established that it does not present any risk to human health and does not have any mutagenic concerns [27]. Additionally, many medicinal drugs incorporate the piperidine structure (Fig. 1), such as the broad-spectrum anticonvulsant drug piperine [28], the antibiotic drug cycloheximide [29], the antitumor drug alecensa [30,31], and the neurological drug rimegepant [32]. Recent studies have demonstrated that piperidines are both effective and safe to use in biochemical preparations. For example, Liu *et al.* prepared pyrimidine piperidine compounds, the majority of which demonstrated good antitumor activity ($IC_{50} = 0.02–0.97$ mg/L) and showed a superior safety profile ($IC_{50} > 10$ mg/L in enzyme-linked immunosorbent assay) [17]. Zhang *et al.* have prepared certain piperidine compounds that possess remarkable anti-tumor properties. Furthermore, research has revealed that these compounds do not have any direct negative impacts on the central nervous system [18]. Some heterocyclic compounds containing piperidine also exhibit strong activity. For instance, paichongding and its analogs show excellent insecticidal activity [33,34]. Moreover, paichongding is capable of overcoming the resistance of existing agents and has excellent systemic features and suitable field stability. And tetrahydro-γ-carboline derivatives exhibit enhanced antibacterial and pharmaceutical activities [35].

Piperidine has been widely utilized in the synthesis of small molecules in the pharmaceutical and pesticide industries, yet between 2010 and 2023, there have been less than 100 reports concerning its structure in the pesticide field. Of these, piperidine compounds have mainly been used for fungicidal (bactericidal) and insecticidal purposes, whereas herbicides, antivirals, and plant growth regulators have been employed to a lesser extent (Fig. S1 in Supporting information). It appears that, although there are reviews on the synthesis and pharmaceutical applications of piperidine compounds in the literature [1,36-39], there is no all-encompassing report on their use in pesticides, both domestically and internationally. This review further summarizes the biological activities of piperidine compounds in fungicidal, insecticidal, antiviral, herbicidal, and plant growth regulators aspects since 2010, and discusses the SARs and the mechanisms of action. Our aim is to provide useful information and explore the potential effects of introducing a piperidine group to develop a novel pesticide in this class of compounds, which is of great significance.

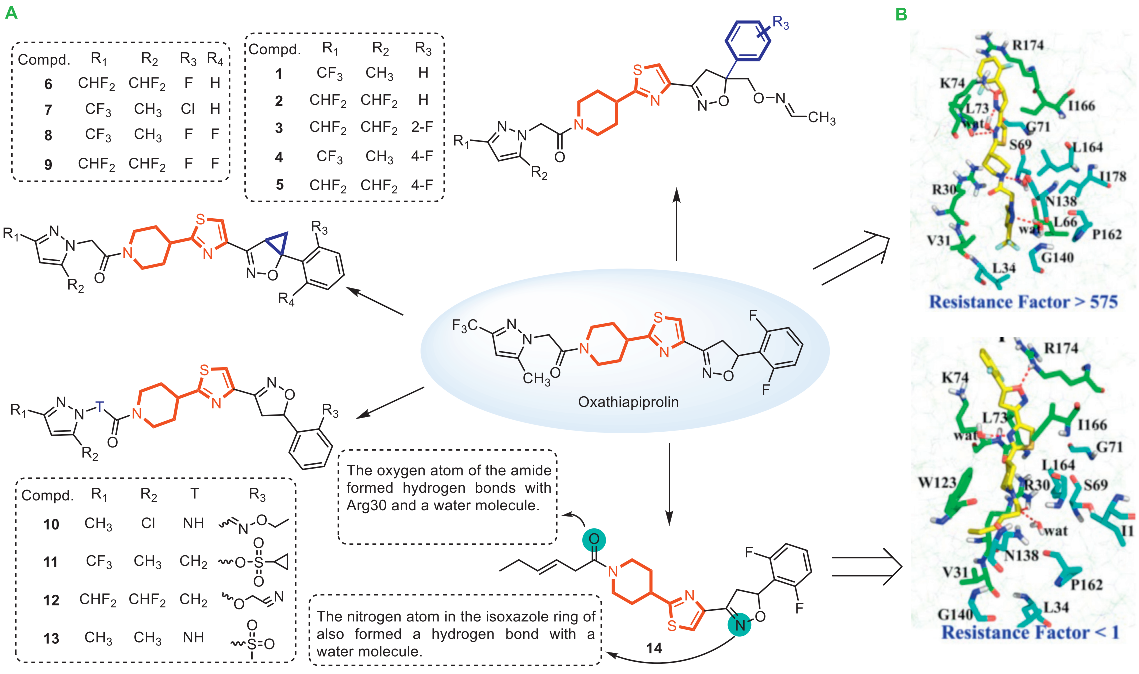
2. Antifungal and antibacterial activity

Through the scientific utilization of fungicides, it is possible to increase the effectiveness of chemical control of plant diseases, as well as to maximize the economic, ecological, and social benefits of chemical control, owing to issues concerning resistance, which has led to increased doses being administered, and pressured on environmental protection. To ensure sustainable agricultural development, it is essential to create fungicides with novel mechanisms of action and environmental synergy that demonstrate high effectiveness. A selection of commercial fungicides (bactericides) that contain piperidine exist, such as zhongshengmycin [40], fenpropidin [41,42], oxathiapiprolin [19], and fluoxapiprolin [43] (Fig. S2 in Supporting information). The Institute of Biophyplaxis of the Chinese Academy of Agricultural Sciences has achieved success in creating a new agricultural antibiotic, known as zhongshengmycin. This antibiotic is derived from *Streptomyces lavendulae* var. *hainanensis* and is classified as an *N*-glycoside alkaline water-soluble substance [44,45]. Zhongshengmycin inhibits pathogenic bacteria mainly by inhibiting the synthesis of bacterial proteins, and also has a strong inhibitory effect on fungal spore formation and germination [46]. It also interacts with plants to increase the activity of major enzyme systems of plant defense reactions such as phenylalanine ammonia lyase, lipoxygenase, and chalcone synthetase, and to induce plant disease resistance. Fenpropidin, a piperidine fungicide created by Syngenta, works by blocking the ergosterol biosynthesis at the reduction and isomerization stages. It is known for its systemic qualities, which enable it to provide protection, curative, and eradicative effects [41,42]. Furthermore, it is capable of conducting in the xylem. Commonly used to control mildew and rust in cereal crops, this fungicide is a reliable solution. For the first time, DuPont declared in 2008 the development of the fungicide oxathiapiprolin, which is effective against oomycete pathogens [47–50]. Its novel and distinctive mechanism of action is to impede the oxysterol-binding protein (OSBP) of pathogenic bacteria [51], OSBP localizes to endoplasmic reticulum-Golgi contact sites, where it transports phosphatidylinositol-4-phosphate and cholesterol, and activates lipid transport and biosynthesis [52,53]. Oxathiapiprolin is also a chiral fungicide containing a pair of enantiomers [54]. Studies of molecular docking and toxicokinetics revealed that the binding of *R*-(-)-oxathiapiprolin to OSBP was stronger than that of *S*-(+)-oxathiapiprolin to OSBP. Additionally, an enantioselective degradation study on tomatoes and peppers under field conditions showed that *R*-(-)-oxathiapiprolin was preferentially degraded. However, oxathiapiprolin was discovered to be a novel chemical inducer, it can inhibit *Arabidopsis* against *Pseudomonas syringae* pv. *tomato* strain DC3000. This is achieved through an increase in callose deposition, H_2O_2 accumulation, salicylic acid and jasmonic acid production, and the related signaling pathway disease resistance [55].

Research scholars have taken a keen interest in piperidine-thiazole-isoxazolines, the core backbone of oxathiapiprolin, and the creation of thiazolyl piperidine drugs has become a new trend. Following the development of oxathiapiprolin, Bayer created a second fungicide, fluoxapiprolin [21,43], in 2012. This fungicide is structurally similar to oxathiapiprolin and its target of action is OSBP. Additionally, it has remarkable fungicidal activity [56]. The fungicidal activity of fluoxapiprolin was determined to be greater than 75%, when tested at 0.20 mg/L against *Phytophthora infestans* (*P. infestans*) and *Plasmopara viticola* (*P. viticola*). Following this, Syngenta and Bayer developed thiazolyl piperidine analogs and filed multiple patents. Introducing an aromatic ring next to the isoxazoline, compounds **1–5** (Fig. 2) exhibited more than 80% preventive activity against *P. infestans* when tested at 200 mg/L, and also displayed more than 80% curative activity against *P. viticola* at the same concentration [57]. With the introduction of a cyclopropyl group next to the isoxazoline, a curative activity of more than 80% was observed for compounds **6–9** (Fig. 2) when tested against *P. viticola* and *P. infestans* at 200 mg/L [58]. The modifications at these positions increase the spatial site resistance of the piperidine-thiazole-isoxazoline body, which hinders the enhancement of fungicidal activity. It was discovered that a variety of compounds, including **10–13** (Fig. 2) [59], which had modifications made to their pyrazole and benzene rings of oxathiapiprolin, were all 100% effective against *P. infestans* when applied at 10 mg/L.

Since oxathiapiprolind and fluoxapiprolin have been developed, researchers have studied their resistance and mechanism of action in depth. Resistance to fungicides usually involves point mutations or overexpression of target proteins [60], and for the fungicides oxathiapiprolind and fluoxapiprolin, it is a point mutation in the oxysterol binding protein-related protein 1 (ORP1) that leads to their resistance. Multiple point mutations in ORP1 could lead to high oxathiapiprolin resistance in *Phytophthora capsici* (*P. capsici*), *Phytophthora sojae* (*P. sojae*), *P. infestans*, *Phytophthora colocasiae*, *P. viticola*, and *Pseudoperonospora cubensis* (*P. cubensis*), and multipoint mutations in ORP1 can lead to high fluoxapiprolin resistance in *P. infestans* and *P. capsica* [50,61-64], and a moderate risk of resistance to fluoxapiprolin in both species [65]. Li also found positive cross-resistance between fluoxapiprolin and oxathiapiprolin [66]. Later, in the effectiveness against *P. sojae*, oxathiapiprolin inhibited mycelial growth, sporangium formation, oospore production, and zoospore release of *P. sojae*, and enhanced osmotic and cell wall stress responses, possibly due to ultrastructural damage to cell walls or cell cytomembrane structures [67,68]. Qu was the first to document the systemic movement of oxathiapiprolin in pepper plants. When applied to the roots, it is taken up and transported from the roots to the stems and leaves of pepper plants, resulting in a significant decrease in disease on the pepper leaves [69].

Following the fungicides oxathiapiprolin and fluoxapiprolin. Researchers have created a variety of thiazolyl piperidine compounds with unique structures and differing levels of antifungal activity. The literature reveals that substituents can be added to both the 4th and 5th positions of the thiazole ring. In general, single substitutions at the 4 position of thiazole are the most common and have an impressive fungal effect. In 2020, Yang's group established the three-dimensional structure of OSBP from *P. capsic* (*pc*OSBP) [70], and the results revealed that the piperidine-

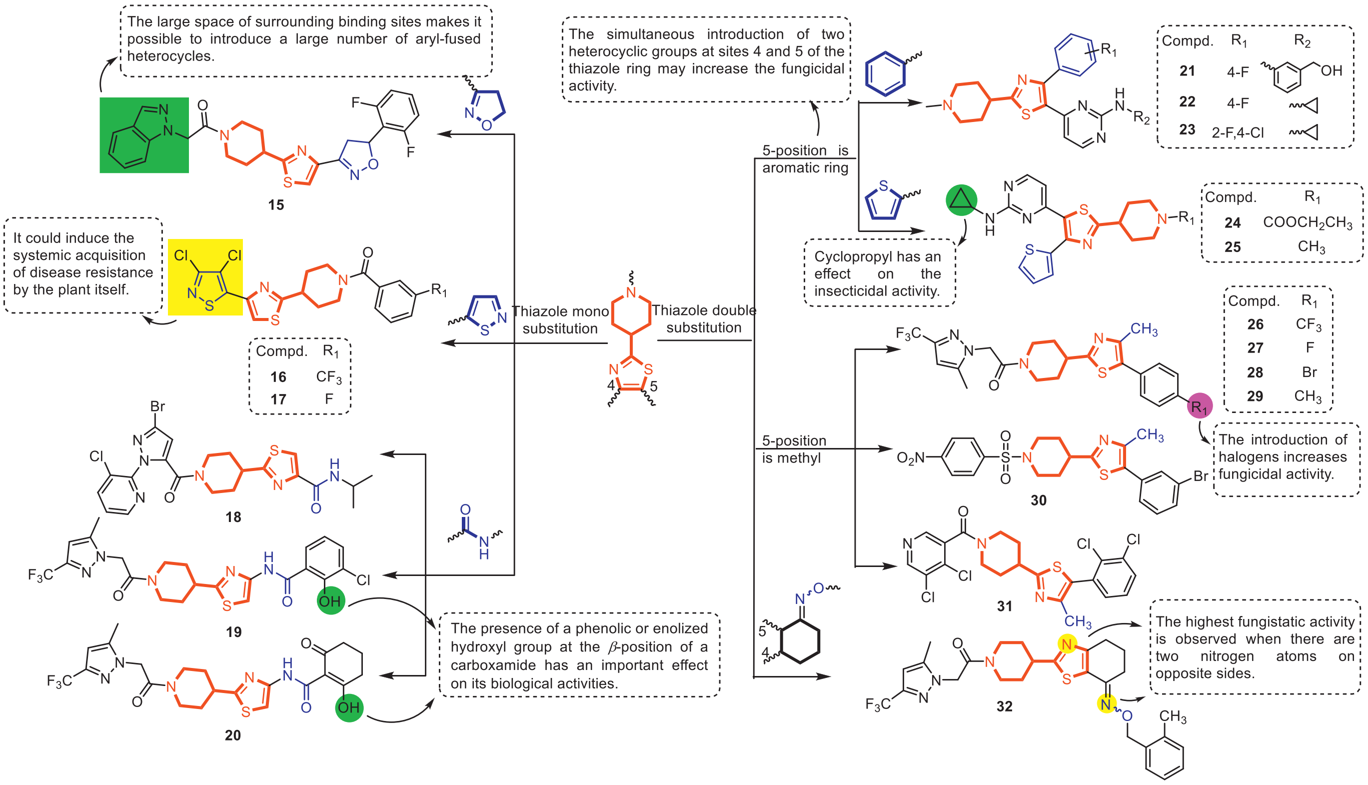


Compd.	R_1	R_2	R_3	R_4
6	CHF_2	CHF_2	F	H
7	CF_3	CH_3	Cl	H
8	CF_3	CH_3	F	F
9	CHF_2	CHF_2	F	F

Compd.	R_1	R_2	R_3
1	CF_3	CH_3	H
2	CHF_2	CHF_2	H
3	CHF_2	CHF_2	2-F
4	CF_3	CH_3	4-F
5	CHF_2	CHF_2	4-F

Compd.	R_1	R_2	T	R_3
10	CH_3	Cl	NH	
11	CF_3	CH_3	CH_2	
12	CHF_2	CHF_2	CH_2	
13	CH_3	CH_3	NH	

Fig. 2. (A) Thiazolylpiperidine compounds (**1–14**) with antifungal (antibacterial) activity. (B) The binding modes of oxathiapiprolin and compound **14** to *pc*OSBP. This panel was reproduced with permission [70]. Copyright 2019, Elsevier.



The large space of surrounding binding sites makes it possible to introduce a large number of aryl-fused heterocycles.

It could induce the systemic acquisition of disease resistance by the plant itself.

Compd.	R_1
16	CF_3
17	F

The presence of a phenolic or enolized hydroxyl group at the β-position of a carboxamide has an important effect on its biological activities.

The simultaneous introduction of two heterocyclic groups at sites 4 and 5 of the thiazole ring may increase the fungicidal activity.

Compd.	R_1	R_2
21	4-F	3-(hydroxymethyl)phenyl
22	4-F	cyclopropyl
23	2-F,4-Cl	cyclopropyl

Cyclopropyl has an effect on the insecticidal activity.

Compd.	R_1
24	$COOCH_2CH_3$
25	CH_3

Compd.	R_1
26	CF_3
27	F
28	Br
29	CH_3

The introduction of halogens increases fungicidal activity.

The highest fungistatic activity is observed when there are two nitrogen atoms on opposite sides.

Fig. 3. Thiazolylpiperidine compounds (**15–32**) with antifungal (antibacterial) activity.

thiazole-isoxazoline of oxathiapiprolin binds to *pc*OSBP, creating a T-cation-π interaction with Arg174 and hydrogen bonds with Leu73, Lys74, Ser69 and water molecules. It was observed that the space of binding sites around the pyrazole ring in the oxathiapiprolin scaffold was larger than the ring itself, thus making it possible to introduce a large number of aryl-fused heterocycles. By modifying the pyrazole group of oxathiapiprolin, compound **14** (Fig. 2) was created. This compound binds to *pc*OSBP, forming an edge-to-edge cation-π interaction with Arg174 and hydrogen bonds with Arg30, Arg174, and water molecules, and it showed a much lower resistance risk (RF $<$ 1) against *P. capsici*. Compound **14** exhibited an *in vitro* inhibitory effect of over 70% when tested at 1 mg/L against *P. capsici*, *P. infestans*, and *Peronophythora litchi*. Following two more rounds of optimization, compound **15** (Fig. 3) was discovered to possess remarkable antifungal activity against *P. capsica* (90.40%) *in vitro* and *P. cubensis* (98%) *in vivo*, at the minimal dosages of 0.01 mg/L and 0.21 mg/L respectively, thus making it comparable to oxathiapiprolin. Moreover, at 25 g/ha, compound **15** was almost as effective as oxathiapiprolin in controlling *P. cubensis* in the field, with 72.40% and 78.30% efficacy respectively [71]. Following this, a 3,4-dichloroisothiazole ring with inducible activity was introduced, which was incorporated into the thiazolyl piperidine backbone. Compounds **16** and **17** (Fig. 3) revealed noteworthy efficacy *in vivo* against *P. cubensis* (100% and 60%, respectively) and *P. infestans* (80% and 30%, respectively), when administered at a concentration of 1 mg/L. Through the analysis of *pr1* and *npr1* in Arabidopsis thaliana, it was determined that the addition of 3,4-dichloroisothiazole ring could lead to the plant acquiring systemic disease resistance on its own. Compound **17** showed an impressive broad-spectrum fungicidal activity, particularly against *Sclerotinia sclerotiorum* (*S. sclerotiorum*) (half maximal effective concentration (EC_{50}) = 0.30 mg/L, more than 10 times more active than oxathiapiprolin and azoxystrobin *in vitro*), and satisfactory activity against *Botrytis cinerea* (*B. cinerea*), *Cercospora arachidicola*, and *Gibberella zeae* (*G. zeae*). Simultaneously, quenching studies demonstrated that OSBP was the target of compound **17** [72]. Researchers discovered compound **18** (Fig. 3), which had 93.75% inhibition activity against *Rhizoctonia solani* (*R. solani*) at 50 mg/L [73]. Furthermore, compounds **19** and **20** (Fig. 3) showed 100% bactericidal activity at 6 mg/L against both *P. infestans* and *P. viticola*, while the SARs revealed that the function of a phenolic or enolized hydroxyl group at the β-position of a carboxamide had an important effect on their biological activities to better control foliar diseases of the *P. infestans* and *P. viticola* [74]. Simultaneously introducing two heterocyclic groups to the 4th and 5th sites of the thiazole ring could potentially lead to an increase in fungicidal activity. In 2010, Won-Sik Choi's group identified compound **21** (Fig. 3) as having a strong fungicidal action against *P. capsici*, with an EC_{50} of 1.03 mg/L [75]. The hydroxymethylphenyl of compound **21** was replaced with cyclopropyl, forming a new structure, compound **22** (Fig. 3). This new compound demonstrated a greater effect against *P. capsici*, with an EC_{50} of 1.01 mg/L [76]. Subsequently, modification of the 4-position of the thiazole ring revealed another increase in the effect of compound **23** (Fig. 3) against *P. capsici* with an EC_{50} of 0.98 mg/L [77]. Notably, compound **23** showed a remarkable insecticidal activity against *Culex pipiens pallens* (*Cx. P. pallens*), and its LC_{50} was 0.51 mg/L. Further modification of the 4-position of the thiazole ring by replacing the benzene ring with thiophene yielded compounds **24–25** (Fig. 3), which had enhanced inhibitory activity against *P. capsici* with EC_{50} of 0.94 and 0.96 mg/L, respectively. With the exception of compound **23**, compounds **21–25** did not demonstrate any insecticidal activity on *Cx. P. pallens* [78]. According to compounds **21–25**, It was determined that the fungicidal activity of *P. capsici* could be augmented in three ways: the introduction of a cyclic amine group on the pyrimidine ring; the maintenance of the *N*-methylpiperidine structure; and the inclusion of a haloaryl group on the thiazole ring. However, by adding an electron-donating group (CH_3) and a heterocyclic group to the

4th and 5th positions of the thiazole ring in double substitution, it has been seen to lead to a relatively weakened fungal effect. This was demonstrated by Ding *et al.* in their synthesis of compounds **26–31** (Fig. 3). Of these, compounds **26–29** showed superior fungicidal activity against *Diplocarpon mali* (*D. mali*) and *B. cinerea*, while compound **30** exhibited inhibitory activity against *P. cubensis*. Additionally, compound **31** displayed broad-spectrum bactericidal activity, with marked inhibitory activity against *G. zeae*, *D. mali*, *P. infestans* and *P. cubensis* [79–81]. Piperidine-thiazole-isoxazoline is the core skeletal structure in which the thiazole ring and the isoxazoline ring are close to a coplanar position, with the nitrogen atoms on the thiazole and the isoxazoline on the same side, and the bonds between the two rings free to rotate. Some discovered that compound **32** (Fig. 3) had the greatest *in vitro* inhibitory activity against *P. capsici* ($EC_{50} = 0.01$ mg/L), when the authors opened the isoxazoline ring with two carbon atoms and attached it to the thiazole ring, with the two nitrogen atoms opposite each other. This was more effective than dimethomorph ($EC_{50} = 0.11$ mg/L) and mandipropamid amide ($EC_{50} = 0.04$ mg/L). Additionally, the compound could cause mycelial abnormalities of *P. capsica* [82]. The SARs indicated that compounds with two nitrogen atoms on the same side were significantly less active than compounds with two nitrogen atoms on opposite sides. In comparison to the commercial drug oxathiapiprolin, the activity of these compounds is noticeably lower, and our speculations on this are the following: (1) connecting the thiazole ring with a flexible group piperidine is necessary; (2) taking out isoxazoline will have an effect on its activity; (3) too much steric hindrance can have an impact on activity.

In order to better analyze the SARs of these piperidine compounds, we selected *Phytophthora infestans* (*P. infestans*) as a research model and some representative compounds to serve as ligands. The binding pocket region of *P. infestans* OSBP (*Pi*OSBP) was defined from the literature [70], and the interaction forces between the ligands and *Pi*OSBP were evaluated through molecular docking (Figs. S3 and S4 in Supporting information). Combine the docking results to analyze their SARs: (1) amino acid residues such as Gly690, Leu692, and Ser688 form hydrogen bonds with the H of the flexible group piperidine, and amino acid residues such as Lys693, Ile785, and Pro694 form hydrophobic interactions with the flexible group piperidine. The more amino acid residues interact with piperidine, the more likely it is to increase the activity of the compound; (2) compounds with higher activity typically have a boat form conformation of the piperidine ring; (3) Leu783 plays an important role in the molecular docking of compounds, it can form interactions with multiple sites in the piperidine-thiazole-isoxazoline-phenyl groups of the compounds and bind these groups tightly together, contributing to increased activity; (4) from the docking results, the binding site of *Pi*OSBP is long and narrow. Therefore, when two groups are simultaneously attached at positions 4 and 5 of the thiazole ring, these compounds have a large spatial site resistance in the active pocket of *Pi*OSBP, which is not beneficial for increased activity. There are significant limitations in the structural modification of oxathiapiprolin. In summary, most of this class of piperidine compounds are substituted at the N1 and C4 positions of piperidine, with the N1 connected to the carbonyl and the C4 to the thiazole, forming a long and narrow structure that is more conducive to binding with *Pi*OSBP. It is evident that the flexibility of the piperidine structure allows for the alteration of its conformation, which can increase the affinity of piperidine compounds for certain targets.

Furthermore, some piperidine compounds also have been found to possess good biological activity. The piperidine compound **33** (Fig. S5 in Supporting information) had an EC_{50} of 3.00 mg/L against *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) [83]. The SARs showed that molecules with the same substituent at different positions of the piperidine ring had varying anti-*Xoo* activities, as evidenced by the fact that the EC_{50} of compounds decreased in the order, 4-methyl piperidine compound (EC_{50} value was 3.00 mg/L) > 2-methyl piperidine compound (EC_{50} value was 3.60 mg/L) > 3-methyl piperidine compound (EC_{50} value was 4.10 mg/L). Simultaneously, the introduction of an electron-donating group on the piperidine ring was beneficial, while the introduction of an electron-absorbing group decreased the biological activity. The 4-quinolone ring, which is the main structural component of a multitude of both natural products and synthetic compounds, has been demonstrated to possess a variety of biological effects, including the inhibition of bacteria. The piperidine compounds **34–38** (Fig. S5) exhibited broad-spectrum fungicidal activity, with inhibition rates of more than 90% at 1 mg/L against Cucumber angular leaf spot, Tobacco bacterial wilt, Potato black leg, Sweet potato bacterial stem, *Xoo*, *Acidovorax citrulli*, Chinese cabbage black rot, *Xanthomonas axonopodis* pv. *manihotis* and *Erwinia amylovora*, which were superior to those of quinoline and zhongshengmycin (<38% inhibition rate) [84]. Additionally, the piperidine compounds **39–42** (Fig. S5) revealed a 90% inhibition of *B. cinerea*, *Colletotrichum graminicola*, *Fusarium moniliforme* and *Fusarium virguliforme* at 0.40 mg/L [85]. Zhang *et al.* showed that the piperidine compounds **43–45** (Fig. S5) exhibited a wide-ranging fungicidal activity, with compound **43** being more effective than Fluopicolide at 50 mg/L against *R. solani*, *Valsa mali* (*V. Mali*), *Gaeumannomyces graminis* (*G. graminis*), *Pythium aphanidermatum* (*P. aphanidermatum*), *Alternaria solani* and *B. cinerea*. Moreover, the EC_{50} values of *R. solani*, *V. Mal*, *G. graminis* and *P. aphanidermatum* were below 10.00 mg/L [86]. Compounds **44–45** displayed a high level of inhibition against *R. solani*, *V. Mali*, *P. aphanidermatum* and *S. sclerotiorum*, with more than 95% inhibition observed at 50 mg/L, and an EC_{50} of 10.00 mg/L or less [87]. The SARs indicate that the absence of no substituent or electron-pushing group on the piperidine ring and no substituent or electron-absorbing group on the benzene ring is essential for the inhibition activity, while the inhibition activity decreases as the electron-absorbing substituent on the benzene ring increases.

3. Insecticidal activity

Piperidine is a fundamental component in the development of novel insecticides. As an illustration, Syngenta developed the piperidine-containing spirocyclic tetronic acid insecticide spiropidion, which functions as a lipid biosynthesis inhibitor. Through inhibiting the activity of acetyl-CoA carboxylase (ACCase) in the process of lipid synthesis in pests, disrupting the synthesis of lipids, thus blocking the normal energy metabolism of the pests and eventually leading to their death. Spiropidion is an environmentally friendly way to control aphids, whiteflies, psyllids, scales, and mites in vegetables and specialty crops [22]. Researchers have been captivated by spiropidion, a novel and effective replacement agent for agricultural production, and have thus optimized its structure, designed and synthesized numerous piperidine spirocyclic compounds. The insecticidal activity of these compounds has been evaluated against *Myzus persicae* (*M. persicae*), *Tetranychus urticae* (*T. urticae*), *Niiaparvata lugens* (*N. lugens*) and *Aphis craccivora* (*A. craccivora*), and it has been observed that piperidine spirocompounds are not only efficient insecticides, but also very friendly to the environment (causing minimal harm to vegetables).

The heterocyclic spirostructure is also regarded as the bioelectronic isoarrangement of certain groups, which can alter the water solubility, lipophilicity, dominant conformation, and ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of the drug molecules to a certain extent, thereby improving the optimized lead molecules to be more drug-like [88]. During the period of 2011 to 2015, a variety of spiropidion compounds

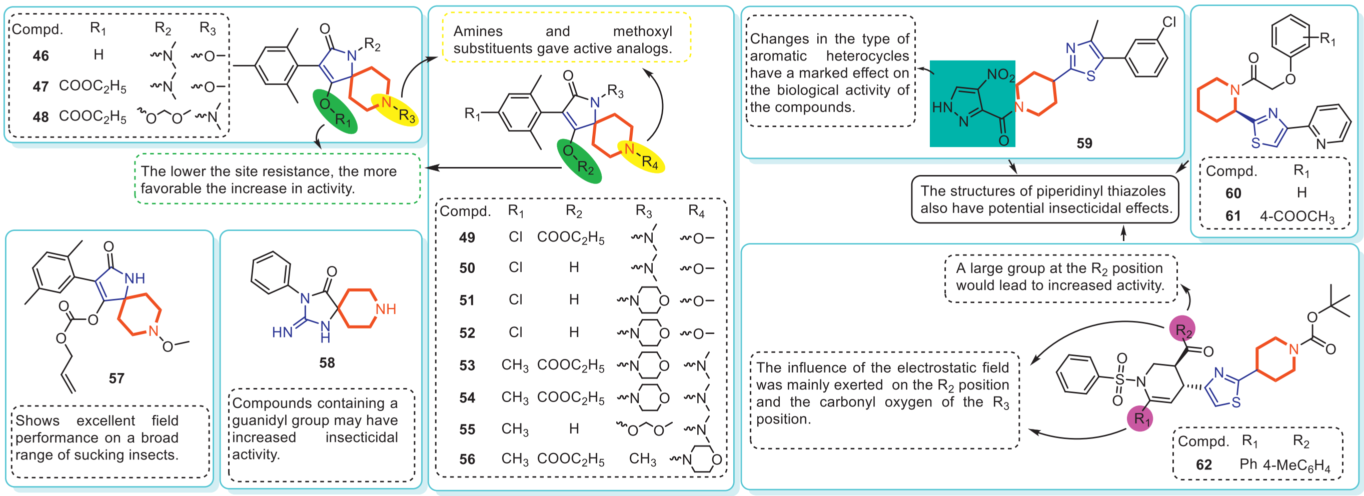
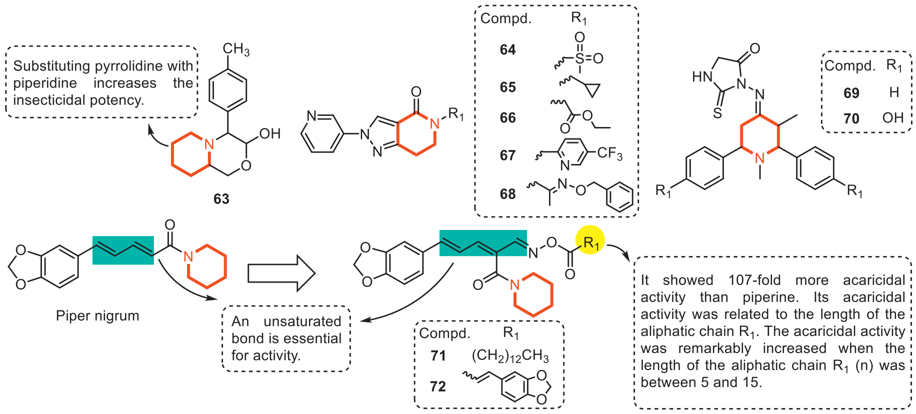


Fig. 4. Piperidine compounds (**46–62**) with insecticidal activity.

were discovered and demonstrated broad-spectrum insecticidal activity. Compounds **46–48** (Fig. 4) were found to have 80%–100% insecticidal activity against *M. persicae*, *T. urticae*, *N. lugens*, *A. craccivora*, *Bemisia tabaci* (*B. tabaci*) and *Thrips tabaci* at 400 mg/L. Furthermore, compounds **49–56** (Fig. 4) showed insecticidal activity (80%–100%) only against *M. persicae* and *T. urticae* at 400 mg/L [89–91]. According to compounds **46–56**, the SARs indicate that a smaller site resistance is more favorable for activity when -OR(H) is attached to the 4-position of the pyrrole ring. Additionally, attaching methoxy and *N,N*-dimethylamine groups to the N1 position of the piperidine is more favorable for obtaining active analogs. Furthermore, compound **57** (Fig. 4) showed respectable field performance against a wide array of sucking pests such as aphids, scales, mites, and whiteflies after foliar applications [22]. Moreover, compound **58** (Fig. 4) displayed 61% insecticidal activity against *M. persicae* larvae at 5 mg/L, and the presence of a guanidyl group may have augmented its insecticidal activity [92].

Thiazolyl piperidine structures are a significant group of pharmaceutical intermediates that possess medicinal properties. Thiazolyl piperidine compound **59** (Fig. 4) had an insecticidal activity of 50% against Mucor at 20 mg/L [93]. Tyagi *et al.* successfully incorporated a chiral modification at the 2-position of piperidine with a thiazole group to create compound **60–61** (Fig. 4), which exhibited higher killing activity against *Brugia pahangi*. Through the target class repurposing method, compound **60** was found to selectively and effectively target both rat and human carnitine palmitoyltransferase 1A with a certain target activity [94]. The SARs demonstrate that the addition of a methyl ester group to the benzene ring increases the hydrophobicity of the compound, which is advantageous for absorption by the nematode cuticle, and the activity is also enhanced. And thiazolyl piperidine compound **62** (Fig. 4) had an insecticidal activity of 60% against aphids at 100 mg/L in 2016 [95]. These findings indicated that thiazolyl piperidine structures have potential insecticidal effects. Apart from this, piperidine heterocyclic compounds have been demonstrated to be effective in insecticidal activity. For example, the piperidine compound **63** (Fig. 5), displayed 93% insecticidal activity against nematodes at 25 mg/L [96]. Therefore, the effectiveness of biological activity can be enhanced through the direct incorporation of piperidine. The SARs show that substituting pyrrolidine with piperidine increases the compound's insecticidal potency against nematodes. Knueppel *et al.* found that piperidine compounds **64–68** (Fig. 5) displayed greater than 80% mortality against *M. persicae* and *B. tabaci* at 200 mg/L [97]. Ibrahim *et al.* introduced thioxoimidazolidin and benzene rings on piperidine to obtain the piperidine compounds **69–70** (Fig. 5). Among others, compound **69** showed good biological activity against larvae of *Culex quinquefasciatus* with an EC_{50} value of 1.37 mg/L, while compound **70** showed good activity against nematodes with an EC_{50} value of 1.57 mg/L [98]. It is worth mentioning that *Piper nigrum* is recognized as the king of spices, and it is a natural and important resource for medicinal resources [99]. Due to the versatility of piperidines, it is possible to change other functional groups to modify the characteristics and effectiveness of the medication. Piperidine is one of the main bioactive components of *Piper nigrum*, with insecticidal activity [100,101]. Piperine oxime ester compounds **71–72** (Fig. 5) (with LC_{50} values of 0.14 mg/L and 0.13 mg/L, respectively) exhibited more than 107-fold piperine acaricidal activity, which was comparable to that of the commercial acaricide Spirodiclofen ($LC_{50} = 0.12$ mg/L). Toxicological studies suggested that the destruction of the cuticle layer crest of *Tetranychus cinnabarinus* by piperine compounds may be the primary cause of their death. It was observed that the acaricidal activity was significantly increased when the length of the aliphatic chain R (n) was between 5 and 15 [102].

Piperidinol is one of the piperidine compounds, and it is the primary component of numerous drugs. Nippon Soda Co., Ltd. studied piperidinol analogs and found that compound **73** (Fig. 6) was 100% lethal to *T. urticae*, *Panonychus citri* (*P. citri*), and armyworm when the concentration was 125 mg/L [103]. Compounds **74** and **75** (Fig. 6) displayed 100% inhibition of *P. citri* and *T. urticae* at the same concentration and were fatal to *Pseudaletia separata* [104]. In 2010, the corporation modified this type of compounds and ascertained that compound **76** (Fig. 6) at 31 mg/L had a powerful effect in suppressing *P. citri* and *T. urticae* by more than 80% [105]. The incorporation of cyclopentane, tetrahydropyran, and cyclohexane structures at the 3- and 5-positions of the piperidine ring has been found to enhance the insecticidal activity, particularly cyclohexane [106]. Consequently, due to the versatility of piperidines, it is possible to attach side chains to modify the characteristics and effectiveness of the medication. Meanwhile, Otsuka Chemical Co., Ltd., ascertained that compound **77** (Fig. 6) had a 100% inhibition rate of *T. urticae* and *P. citri* at 500 mg/L [107]. Additionally, cinnamyl piperidine structures are popularly used in insecticides, and Syngenta has produced a series of compounds that demonstrate insecticidal and acaricidal activity at lower doses. Compounds **78–79** (Fig. 6) were found to be highly lethal to *Spodoptera littoralis* (*S. littoralis*) and *Heliothis virescens* (*H. virescens*) at 200 mg/L, with more than 80% mortality [108]. Sim-

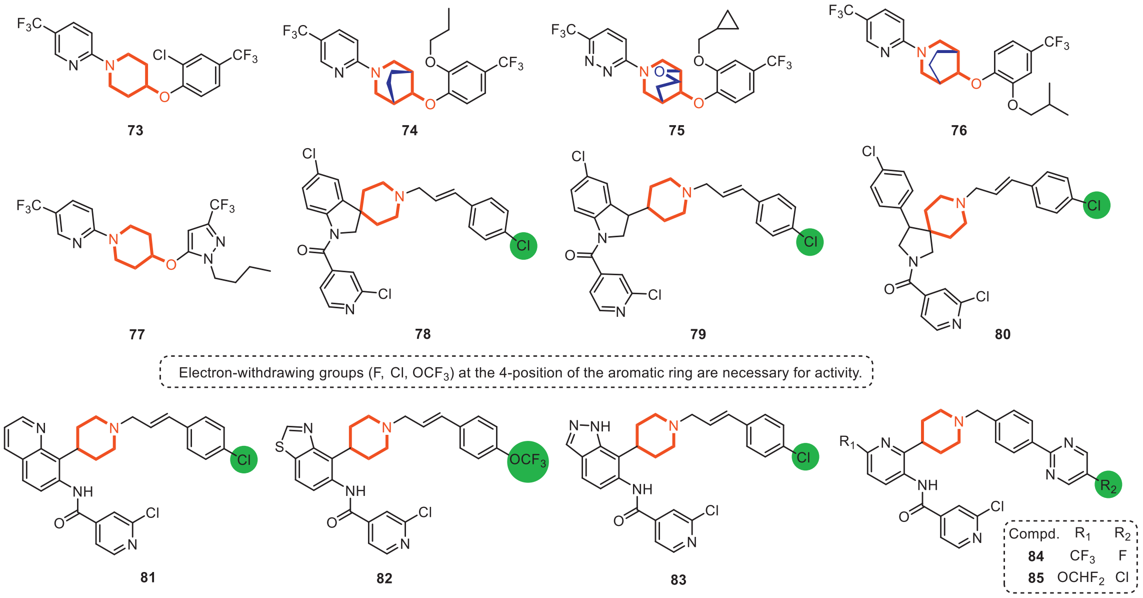


Substituting pyrrolidine with piperidine increases the insecticidal potency.

An unsaturated bond is essential for activity.

It showed 107-fold more acaricidal activity than piperine. Its acaricidal activity was related to the length of the aliphatic chain R$_1$. The acaricidal activity was remarkably increased when the length of the aliphatic chain R$_1$ (n) was between 5 and 15.

Fig. 5. Piperidine compounds (**63–72**) with insecticidal activity.



Electron-withdrawing groups (F, Cl, OCF$_3$) at the 4-position of the aromatic ring are necessary for activity.

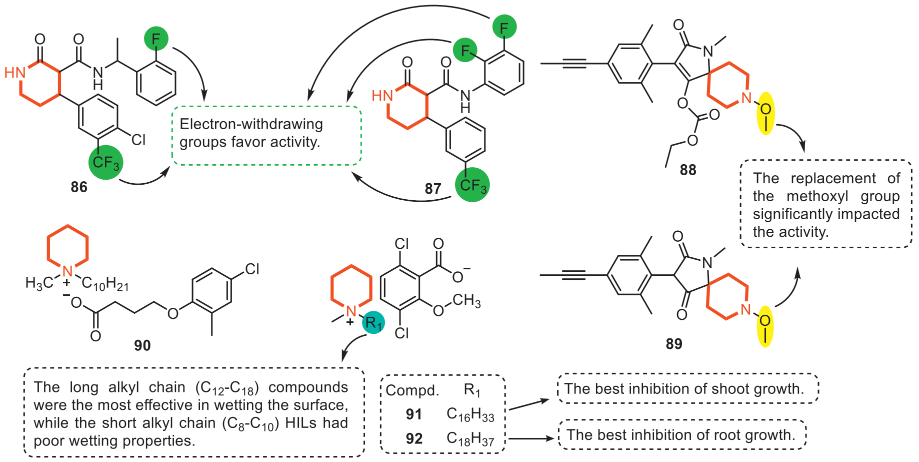
Fig. 6. Piperidine compounds (**73–85**) with insecticidal activity.

ilarly, compound **80** (Fig. 6) was observed to have a greater than 80% mortality rate against *Plutella xylostella* (*P. xylostella*) [109]. Additionally, compounds **81–85** (Fig. 6), which are piperidine compounds, demonstrated good insecticidal activity, with more than 80% control of *S. littoralis*, *H. virescens*, *P. xylostella*, and *Diabrotica balteata* [110,111]. The SARs demonstrate that introducing an electron-withdrawing group (F, Cl, OCF$_3$) to the 4-position of the aromatic ring is essential for improved activity.

4. Herbicidal activity

Piperidine-based compounds are mostly found in patents related to herbicides, there are comparatively few studies in journal form on the subject. Currently, the commercial herbicides containing piperidine include dimepiperate (Fig. S6 in Supporting information) [112], piperophos (Fig. S6) [113], and cypyrafluone [23], which was developed in China. Dimepiperate is a plant endogenous auxin antagonist, disrupting the equilibrium of the endogenous auxin, thereby preventing protein synthesis, halting the growth point cell division, and ultimately resulting in death. It is suitable for use in rice seedling, transplanting, and direct seeding fields to protect from *Echinochloa crus-galli* (*Echcg*) and wire grass [112]. Piperophos is a selective herbicide, entering their systems through the roots, germinal sheaths, and cotyledons of young plants and preventing their growth, ultimately leading to their death. It controls annual gramineous weeds and sedge weeds [113]. Cypyrafluone, the first novel hydroxyphenylpyruvate dioxygenase (HPPD)-inhibiting herbicide for grassy weed control in wheat fields, which was developed by Qingdao Kingagroot Chemicals Co., Ltd. and was put into commercial use in 2018. Cypyrafluone blocks the conversion of its substrate to crystalline by inhibiting the activity of plant corpus HPPD, thus preventing the normal synthesis of tocopherols and plastoquinones, which in turn affects the synthesis of carotenoids in target plants, leading to whitening of target plant leaves and eventual death of the target plant [23]. Noteworthy, cypyrafluone contains the piperidone structure, which is a major component of many natural products and a useful starting point for creating large structures with biological activity. For example, compound **86** (Fig. 7) showed a good herbicidal effect and high selectivity against selected noxious plants [114]. At an application rate of 31 g/ha, compound **87** (Fig. 7) had a significant herbicidal effect (75%–95%) against *Echcg*, *Digitaria sanguinalis*, and *Setaria faberi* (*Setfa*) [115]. Moreover, spiropiperidine compounds **88–89** (Fig. 7) displayed considerable herbicidal activity against *Amaranthus retroflexus*, *Setfa*, *Alopecurus myosuroides*, *Echcg* and *Lolium perenne* [116].

Herbicidal ionic liquids (HILs) are novel ionic liquids defined as organic compounds with a melting temperature below 100 °C,



Electron-withdrawing groups favor activity.

The replacement of the methoxyl group significantly impacted the activity.

The long alkyl chain (C_{12}-C_{18}) compounds were the most effective in wetting the surface, while the short alkyl chain (C_8-C_{10}) HILs had poor wetting properties.

Compd.	R_1
91	$C_{16}H_{33}$
92	$C_{18}H_{37}$

The best inhibition of shoot growth.

The best inhibition of root growth.

Fig. 7. Piperidine compounds (**86–92**) with herbicidal activity.

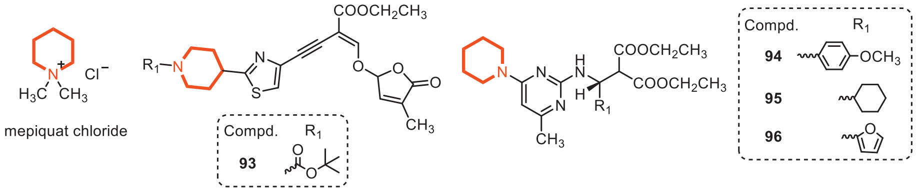


Fig. 8. Piperidine compounds (**93–96**) with plant growth regulating activity and antiviral activity.

that contain ions exhibiting herbicidal activity [117,118]. Their primary purpose is to protect crops by increasing the effect of herbicides while minimizing their environmental hazard. For instance, Juliusz conducted a synthesis of new MCPB-based ionic liquids with a 1-alkyl-1-methylpiperidine cation, and the results showed that the herbicidal efficacy of all the HILs was comparable or better than the commercial herbicides (which was at 70% for MCPA-salt) on common lambsquarters and oilseed rape. Of all the HIL compounds, compound **90** (Fig. 7) with dodecyl chains was the most successful in terms of herbicidal effect and it also showed superior surface active characteristics [119]. The SARs indicated that longer alkyl chains (C_{10}–C_{18}) attached to the N position of piperidine exhibited higher herbicidal activity (80%-95%), whereas those with shorter alkyl chains (C_2–C_9) were less efficient (70%-80%). However, an attractive solution to improve the effectiveness of HILs is a bifunctional herbicidal ionic liquid [120]. Compounds **91–92** (Fig. 7), consisting of amphiphilic cations and anions of novel piperidine-based HILs with potential herbicidal activity. It was the first time that the issue of decreasing mobility of these HILs on the surface of weed leaves was reported. All the HILs presented a higher wettability than commercial dicamba, with piperidines containing long alkyl chain compound **91** being the most efficient in wetting surfaces (weeds and crop leaves), whereas the drops of HILs with shorter alkyl chains (C_8–C_{10}) failed to slide down the leaves. Moreover, all the synthesized piperidinium-based ionic liquids maintained their phytotoxicity. Additionally, compound **92** revealed the most impressive growth inhibiting effect on roots, while compound **91** had the best growth inhibition effect on shoots [121]. This research offers the necessary structural and functional information to create effective crop protection agents for future use.

5. Plant growth regulating activity and antiviral activity

Piperidine compounds have had limited use in plant growth regulators and antiviral applications. Piperidine compounds have a variety of impacts on the regulation of plant growth, with the most common being the inhibition of growth. Mepiquat chloride (Fig. 8) is a well-known plant growth regulator, currently used in agricultural production. It is observed to be effective in inhibiting the biosynthesis of gibberellin [122]. However, compounds containing piperidine are rarely reported as plant growth regulators in recent years. Only an alkyne compound containing piperidine (**93**, Fig. 8) showed remarkable germination inhibition activity on *Arabidopsis thaliana* seeds at 1 mg/L. Additionally, it was also found to be effective in suppressing the germination of common weeds in our farmland [123]. In 2018, Bai *et al.* synthesized chiral piperidine compounds **94–96** (Fig. 8). These compounds showed better curative, protective, and inactivation activities than ningnanmycin against tobacco mosaic virus (TMV) at 500 mg/L. Its SARs revealed that the substitution of aromatic groups could enhance the anti-TMV activity, with the electron donating group at the 4-position on the benzene ring having the greatest impact ($OCH_3 > CH_3 > Cl$) [124]. These chiral products can be used as lead structures for the development of new anti-TMV agents.

6. Summary and outlook

The recent development of agrochemicals containing piperidine structures, such as spiropidion and cypyrafluone, has highlighted the potential of piperidine compounds. This review summarizes and analyzes the pesticide activity of compounds containing piperidine groups. Most of the piperidine-based compounds have been known to exhibit fungicidal and insecticidal properties, although herbicidal activity, antiviral activity, and plant growth regulation have been research reported to a lesser extent. Piperidine, commonly used in the formation of agrochemicals, offers a wide range of structural versatility. The piperidine molecular backbone can be modified to increase its biological effectiveness, depending on the type and location of functional groups. Specific functional groups can be incorporated, or the conformation of the piperidine ring can be modified to enhance the interaction between the piperidine molecule and the receptor or enzyme. This can increase its binding and effect on particular targets, thereby improving drug selectivity and effectiveness. Piperidine has a strong capacity to expand its chemical structure, often serving as a bridge in drug molecules. It has been employed to form a bridged ring to join with other pharmacodynamic structures, resulting in compounds with remarkable biological activity, particularly thiazolyl piperidine compounds. These compounds have been used in commercial fungicides and have shown significant biological activity, and the thiazolyl piperidine structural skeleton is beneficial for further investigations in terms of bacteriostatic and insecticidal activities. Moreover, piperidine can also utilize its own biological activity to derive and synthesize compounds with better biological activity, such as piperidine spirocompounds. These compounds are mostly substituted at the 1 and 4 positions of piperidine. Piperidines have widespread applications in drug development and research. Recent studies have shown that piperidine compounds are neuroprotective and may attenuate neurological damage by reducing disturbances in neuronal dynamics [125]. Additionally, piperidine compounds have been associated with cognitive enhancement [126]. Piperidines are also utilized in drug delivery systems to improve the efficacy of drugs by combining them with other drugs for enhanced drug delivery [127].

So far, while compounds containing piperidine have been assessed for their activity and structure-activity relationships, the mechanism of the active compounds has not been thoroughly explored. As a result, the majority of piperidine compounds have an unclear mechanism (or target) of insecticidal and antibacterial effects, which limits their ability to optimize their structures in depth. In order to find an outlet for piperidine, the development of corresponding pesticides or pharmaceutical and chemical intermediates is an important direction for the development of piperidines. However, if an active ingredient containing piperidine-based can be extracted from natural products, its structure can be optimized and some new varieties can be derived, which may reduce the toxicity of pesticides and improve the safety of crops. In other words, the development of piperidine compounds with novel structures and mechanisms of action has become a hot research topic for the creation of new pesticides.

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

Wei Sun: Validation, Visualization, Writing – original draft, Writing – review & editing. **Anjing Liao:** Investigation, Validation. **Li Lei:** Validation, Visualization. **Xu Tang:** Validation, Visualization. **Ya Wang:** Visualization. **Jian Wu:** Resources, Writing – review & editing, Supervision.

Acknowledgments

The financial support from the National Natural Science Foundation of China (No. 32072445), the Science and Technology Plan Project of Guizhou Province (Qiankehezhicheng[2024] the general 083), the Program of Introducing Talents to Chinese Universities (No. D20023), the Central Government Guides Local Science and Technology Development Fund Projects (Qiankehezhongyindi (2023) 001), the Technology Achievement Transformation (general project) of Guizhou Province (Qiankehechengguo [2022] the general 063), Key Agricultural Technology R&D Projects of the Xinjiang Production and Construction Corps (NYHXGG, No. 2023AA602), the Frontiers Science Centre for Asymmetric Synthesis and Medicinal Molecules, Department of Education, Guizhou Province [Qianjiaohe KY (2020)004], and the specific research fund of The Innovation Platform for Academicians of Hainan Province (No. SQ2020PTZ0009).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109855.

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