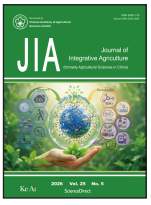
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REVIEW

Recent research progress and outlook on the bioactivities and mechanism of piperazine pesticides

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Highlights

- Research progress on the pesticide biological activities of piperazine derivatives is summarized.
- The mechanism action of the biological activities of piperazine derivatives as pesticides is discussed and analyzed.
- The future directions of pesticide structural derivation and the mechanism action of piperazine derivatives are prospected.

Abstract

Piperazine is a nitrogen-containing heterocyclic compound that is commonly used as an intermediate linking group in the structural derivation of compounds. Heterocyclic drugs containing piperazine have many commercial uses in medicine and are also used in pesticides. For example, the piperazine ring is a key structural element of the systemic fungicide Triforine. Piperazine is an attractive option because of its low acute toxicity to mammals, and it has become one of the hotspots of heterocyclic pesticide research in recent years. The pesticidal activity and mechanism of piperazine derivatives have been studied extensively. Herein, a comprehensive review of the research on the pesticidal bioactivity and mechanism of action of piperazine derivatives from 1971 to 2025 is presented. The agriculturally relevant antifungal, insecticidal, anti-plant virus, herbicidal, acaricidal, and antibacterial activities are discussed and the molecular mechanism of action of related piperazine derivatives is summarized. In addition, we also propose the future derivation direction of piperazine structures and look forward to the development of the anti-plant virus and anti-bacterial action mechanisms.

Keywords: piperazine derivatives, pesticidal activities, structure–activity relationship mechanism of action, research progress

1. Introduction

Due to the continuous growth of the global population and the increasing awareness of the associated environmental and health issues, the demands for agricultural production are becoming greater, together with the requirements for the low toxicity and safety of pesticides. The toxicity of pesticides to non-target organisms (Gibbons *et al.* 2015; Stanley *et al.* 2016; Krupke *et al*. 2017) and environmental pollution (Goulson 2013; Wood and Goulson 2017; Hladik *et al.* 2018) are attracting increasing attention. The extensive and widespread use of pesticides has aggravated many issues associated with resistant diseases and pests. The problems associated with increasing pesticide resistance and the high toxicity of pesticide pollutants such as organophosphates and pyrethroids have gradually led to the reduced use or prohibition of many pesticide compounds (Shu *et al.* 2016). Therefore, developing new pesticides with high efficiency, low toxicity, novel modes of action, high levels of safety, and good environmental compatibility continues to be vital for pesticide research and addressing the problem of pesticide resistance.

Piperazine, also known as hexahydropyrazine, is a nitrogen-containing heterocyclic organic compound with a six-membered diamine ring structure that provides an ideal nitrogen-rich framework for bioactive compounds. Piperazine itself has good insecticidal and anthelmintic activities. Piperazine citrate can paralyze ascaris muscles and has an excellent medicinal effect in the removal of ascaris. Piperazine derivatives not only have a wide range of applications in medicine but also provide active intermediates for producing pesticides (Wu and Ling 2016). Piperazine

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exhibits extensive biological activities, including anti-inflammatory (Palaska *et al.* 1993; Silva *et al.* 2015; Huang *et al.* 2019), anticancer (Mistry *et al.* 2017; Gao *et al.* 2019), antitumor (Sun *et al.* 2015; Mao *et al.* 2016), antioxidant (Mohammadi *et al.* 2015), antituberculosis (Zhang and Aldrich 2019; Deshmukh *et al.* 2020), antibacterial (Patil *et al.* 2019; Yıldız 2020), anticonvulsant (Novack *et al.* 1978), weed-killing (Wu *et al.* 2012a), insecticidal (Zhang *et al.* 2018a), and antiviral (Reddy *et al.* 2013; Yu *et al.* 2015) actions. Many commercial drugs contain the piperazine structure (Fig. 1). For example, the systemic fungicide Triforine, which was developed in 1969 by Celamerck (Germany), is toxic to numerous fungi in many families of Basidiomycetes, Ascomycetes, and Deuteromycetes, and it is used to manage a variety of plant diseases, such as powdery mildew on fruits (especially strawberries), trees, cucumbers, and peas (Fuchs *et al.* 1971). The application of Triforine to the roots of cucumbers, rye, wheat, or barley can provide systemic protection against powdery mildew infection (Fuchs *et al.* 1971).

Structure–activity relationship studies have shown that the -$CC1_3$CHNHCHO moiety may be an important active group (Carter *et al.* 1972). Studies on the relationship between the structures of Triforine and Chloraniformethan and their fungicidal activity against barley powdery mildew using root immersion or leaf spray application indicate that the structure of XCHNHCO (where X is sulfur, nitrogen, or oxygen) is a prerequisite for activity (Brown and Woodcock 1975). Studies on the mechanism of action of these compounds revealed that Triforine inhibits the biosynthesis of ergosterol and prevents fungal cell wall synthesis (Sherald and Sisler 1975). Triforine dissipation and degradation studies in soil and strawberries showed that this compound is easily dissipated in strawberries with a half-life of 3.53–4.42 days, and the final residue (0.032–0.264 mg kg^{-1}) is lower than the maximum allowable residue (1 mg kg^{-1}) (Zhang *et al.* 2014). To date, there has been no comprehensive review of piperazine derivatives in the field of pesticides. Herein, we summarize the progress that has been made in the research and application of piperazines as pesticides. Our previous review of vanillin (Lou *et al.* 2024) and our experience in pesticide research (Wei *et al.* 2024; Zhang A W *et al.* 2024; Wang *et al.* 2025) provide support for this review. We aim to provide a reference for the design of piperazine and its structural derivatives in the field of pesticides and discuss the mechanism of action of these compounds.

2. Research on piperazine derivatives

2.1. Insecticidal activity

Pests cause major economic losses in agricultural production. However, the use of pyrethroids, carbamates, and organophosphorus insecticides has become increasingly problematic in recent years because of the associated environmental pollution and resistance problems. Some highly damaging pesticide pollutants have been banned. Therefore, the research and development of new, high-efficiency, green pesticides that are less toxic and more environmentally friendly are urgently required. The development and use of piperazine derivatives as insecticides have progressed, possibly because piperazine itself has insecticidal and anthelmintic activities, and piperazine derivatives can exhibit even greater insecticidal activity.

Compound **1** (Fig. 2) exhibits up to 94.4% fly killing activity in 24 h at 1,000 mg L^{-1} (McGrath 1960). Piperazine-carbon disulfide complex **2** (Fig. 2) is very effective against cockroaches (Fondren 1964). When the R group is methyl, the series of compounds **3** (Fig. 2) are effective against roaches, ticks, beetles, helminths, as well as *Rhizopus nigricans*, *Pllularia pullulans*, *Aspergillus terreus*, and potato and tomato late blight (Dunbar 1965). In the series of compounds **4** (Fig. 2), the activity against nematodes is 100% at 125 mg L^{-1} when R is Cl or Br (Tetenbaum and Degginger 1972). The series of compounds **5** (Fig. 2) exhibit good insecticidal activity against green peach aphid (*Myzus persicae*) and black bean aphid (*Aphis fabae*) (Fancher 1980). The activity against tobacco budworm (*Heliothis virescens*) of 100 mg L^{-1} of compounds **6a** and **6b** (Fig. 2) was 100% when delivered by feeding methods, and 95 and 90%, respectively, using the foliar spray method (Silverman *et al.* 1997). Piperazine 4′′-alkylene Avermectin derivatives **7a** and **7b** (Fig. 2) exhibit good insecticidal activity, with moderate and identical growth inhibitory actions against the free-living nematode *Caenorhabditis elegans* and brine shrimp *Artemia salina*, with minimum inhibitory concentrations (MIC) of 10 and 2 ng mL^{-1}, respectively. Preliminary activity *in vitro* tests showed that **7a** exhibits insecticidal activity comparable to that of Avermectin (Fig. 2) against *Ctenocephalides felis*, *Boophilus microplus*, *Periplaneta americana*, *Musca domestica*, and *Lucilia cuprina* (Nagai *et al.* 2003).

Piperazine derivative **8** (Fig. 2) exhibits good inhibitory activities on the peristalsis of *Haemonchus* twitch larvae at 0.01 mmoL L^{-1} (Lee *et al.* 2005). Compounds **9a**–**d**, **10a**, and **10b** (Fig. 2) exhibit good insecticidal activity, with inhibition rates against Egyptian cotton leafworm (*Spodoptera littoralis*), *H. virescens*, and *M. persicae* that are greater than 80% at 80 mg L^{-1}, inhibition rates against diamond back moth (*Plutella xylostella*) of more than 80% at 18.2 mg L^{-1}, and inhibition rates against yellow fever mosquito (*Aedes aegypti*) of more than 80% at 2 mg L^{-1} (Cassayre *et al.* 2005). Insecticidal activity tests against *H. virescens* showed that a concentration of 0.25 mmol L^{-1} is required. Compared with the growth of *H. virescens* in the untreated control, 100% growth inhibition rates were exhibited by **11a**–**c** (Fig. 2) (Barron *et al.* 2006). The *N*-substituted piperazine derivatives **12a**–**c** (Fig. 2) exhibited inhibition rates of 50–100% against fruit fly (*Drosophila melanogaster*) and cotton aphids (*Aphis gossypii*) at 4,000 and 200 mg L^{-1}, respectively. Compounds **13a**–**c** (Fig. 2), **14a**, **14b**, and **15** (Fig. 3) exhibited inhibition rates of 50–100% at 25 mg L^{-1} against wheat glume blotch (*Leptosphaeria nodorum*) and wheat leaf blotch (*Mycosphaerella graminicola*) (Lorsbach *et al.* 2007). Serotonin (5-HT) exerts significant effects on vertebrates and invertebrates by interacting with receptors. Compounds **16a** and **16b** (Fig. 3) have good activity against armyworm *Pseudaletia separata* Walker, with growth inhibition rates of 77.7 and 73.6%, respectively, at 500 mg L^{-1}. The activities of compounds **16a** and **16b** against insects may be related to

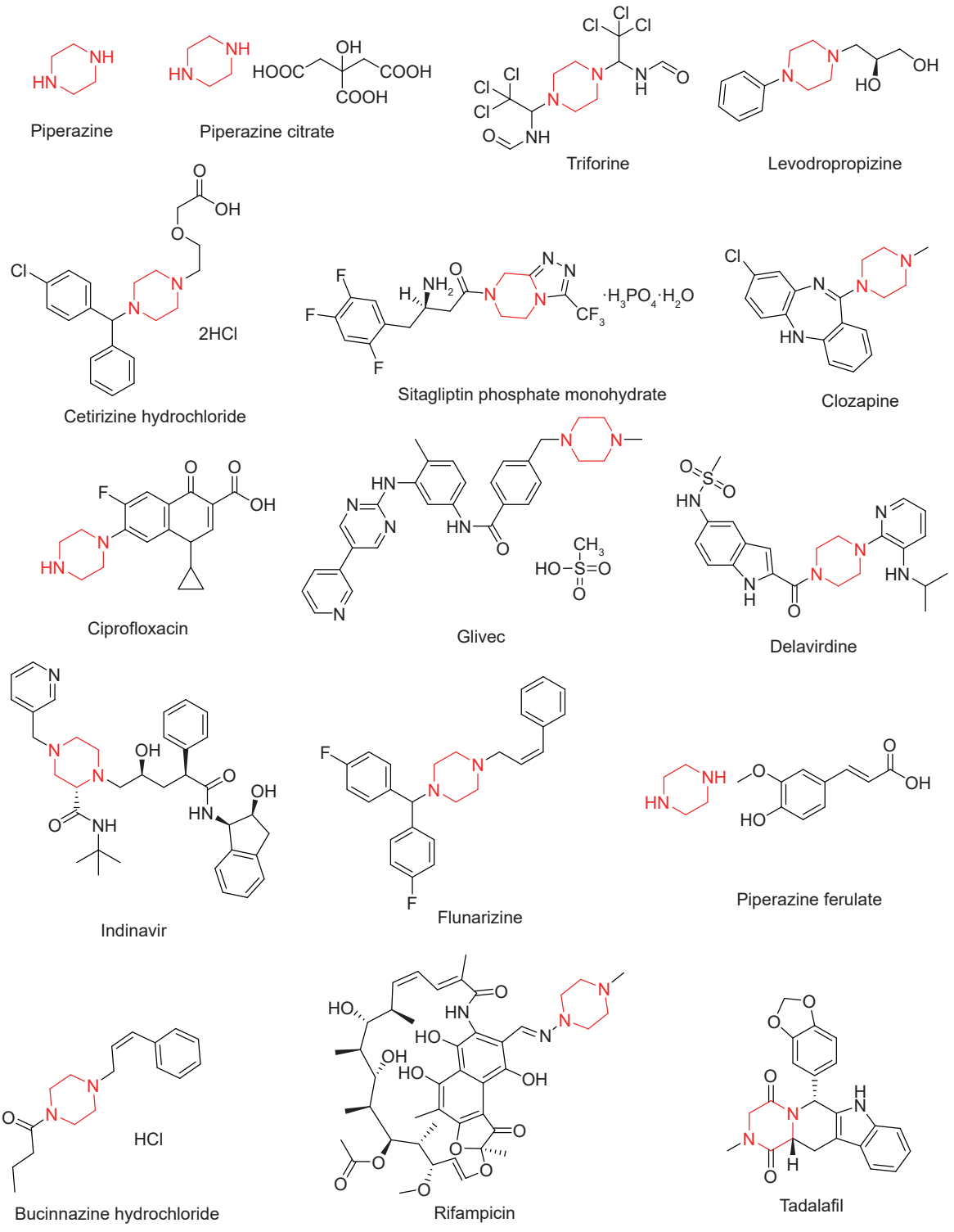


Fig. 1 Commercial drugs containing the piperazine structure.

their 5-HT_{2A} receptor interaction, and they could act as 5-HT_{2A} receptor antagonists (Cai *et al.* 2008).

Pyridine (thiazole) methyl-containing piperazine compounds possess good insecticidal activity against *Culex pipiens* but weaker herbicidal and insecticidal activities against *A. fabae*. For example, compound **17** (Fig. 3) exhibits 100% activity against *C. pipiens* at 50 mg L^{-1}. Structure–activity relationship (SAR) studies revealed that the activity of the thioamide is higher than that of the amide, and that the amide has almost no activity (Li *et al.* 2008). The piperazine derivative **18** (Fig. 3) has been studied as a pest control agent and was found to exhibit efficient and stable pest control effects (Ogawa *et al.* 2008). Compound **19** (Fig. 3) showed at least 80% activity against *C. felis* at a concentration of ≤5 mg L^{-1} (Schnatterer *et al.* 2008). The aryl-substituted piperazine compounds **20a–c** (Fig. 3) were tested

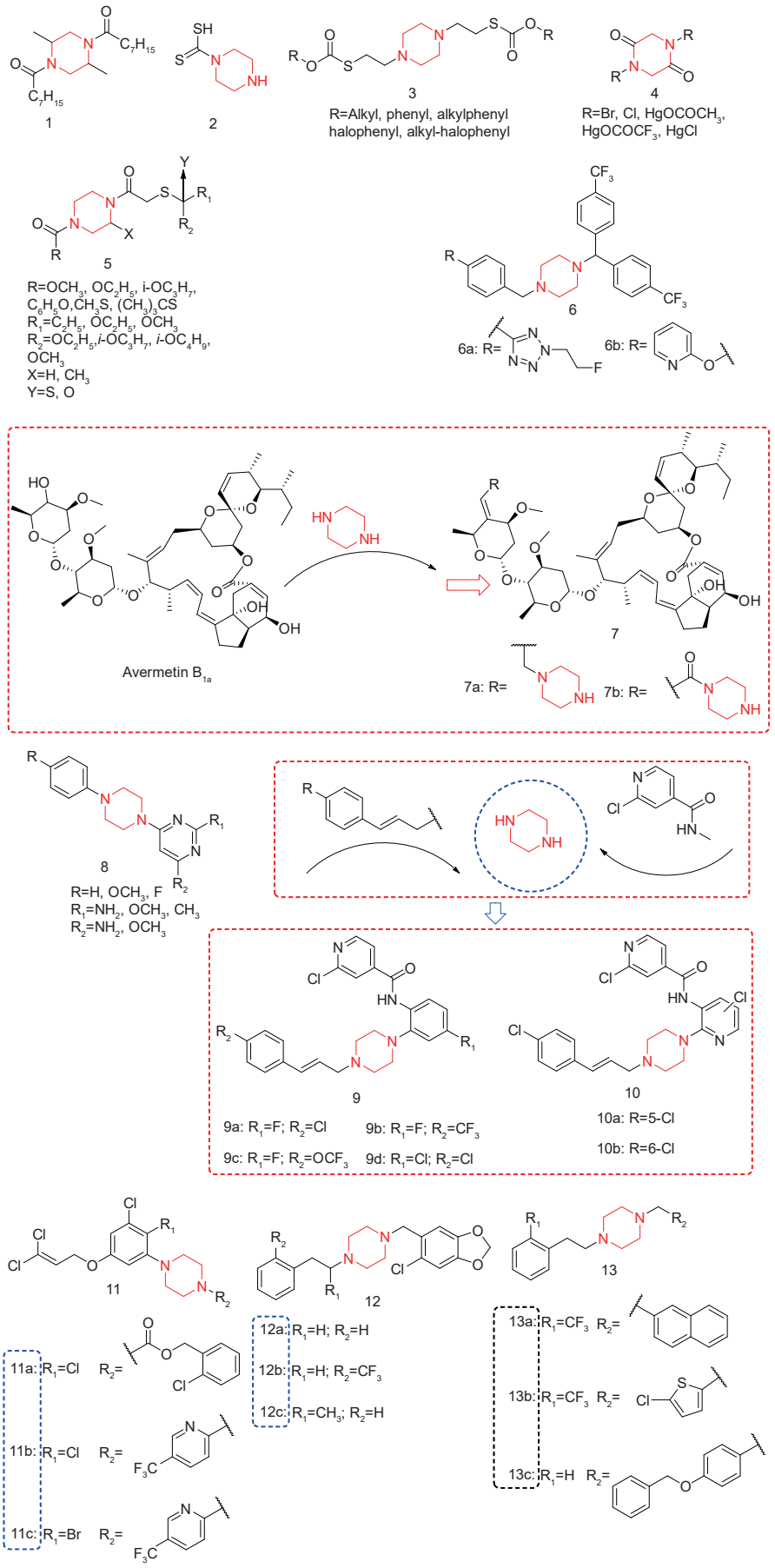


Fig. 2 Chemical structures of Avermetin B_{1a} and piperazine derivatives (1–13) with insecticidal activity.

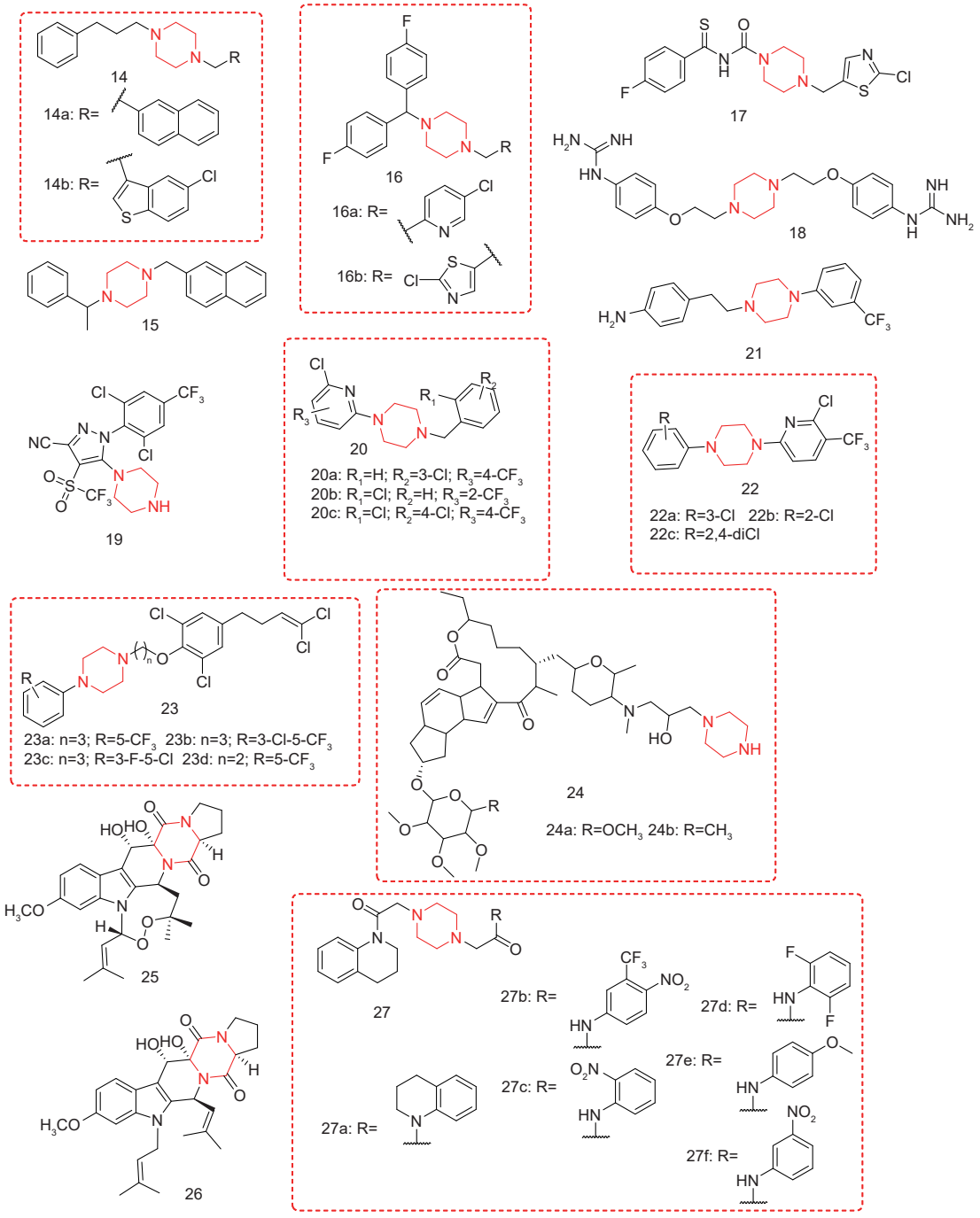


Fig. 3 Piperazine derivatives (14–27) with insecticidal activity.

against armyworm *P. separata* Walker at 500 mg L^{-1} and found to have good activity, with mortality rates of 100, 93.3, and 93.3%, respectively. The aryl-substituted piperazine derivatives have been used to study insect pentahydramine receptors. The inhibitory activities of these compounds on lepidopteran insects not only advances our understanding of insect pentahydramine receptors but also lays the foundation for a new type of green pesticide that operates through a previously unexplored mechanism (Li *et al.* 2009). By using **21** (Fig. 3) derived piperazine as a serotonergic ligand, the application of compounds **22a–d** (Fig. 3) led to the death of armyworm *P. separata* Walker within 72 h at 500 and 250 mg L^{-1}, which indicates that compound **21** may be a lead compound as a 5-HT receptor antagonist for the effective treatment of pests (Cai *et al.* 2010).

Piperazine-containing dihalopropene ether compounds have excellent insecticidal activity against *P. xylostella*, *Spodoptera exigua*, and *A. gossypii*. The insecticidal activity of compound **23c** (Fig. 3) against *P. xylostella* is 80% at 600 mg L^{-1}, and the insecticidal activities of compounds **23a–c** (Fig. 3) for *P. xylostella* are all 100%. The insecticidal activities of compound **23b** against *P. xylostella* are 100 and 75% at 6.25 and 1.56 mg L^{-1}, respectively, which are higher than those of the control, Pyridalyl (90 and 50%,

respectively). When the same substituent is connected to one of the piperazine NH groups, the introduction of Cl or CF_3 groups at the second NH group enhances the insecticidal activity; and when one NH of piperazine is replaced or both NH are replaced simultaneously, the insecticidal activity is significantly reduced (Liu *et al.* 2010). The piperazine-containing spinosyn derivatives **24a** and **24b** (Fig. 3) have insecticidal activity against many insects and mites, especially cotton red spiders and armyworms (Liu *et al.* 2011). For compounds **25** and **26** (Fig. 3), which were isolated from metabolites of *Aspergillus fumigatus*, the antifeedant index for armyworm larvae (*Mythimna separata* Walker) reached 55.0 and 50.0%, respectively. These compounds may be important components of *A. fumigatus* which have antifeedant properties and antifungal activity and may protect the host from pathogens and pests (Li *et al.* 2012). Compound **27a** (Fig. 3) has no insecticidal activity against aphids or spider mites at 600 mg L^{-1} but exhibits insecticidal activity against *S. exigua*, armyworm, cotton bollworm, and corn borer. The inhibition rates for *P. xylostella* were 100 and 75% at 600 and 200 mg L^{-1}, respectively, which are comparable to those of the control pesticide, Thiamethoxam. Thus, further research on **27a** may establish it as a natural lead compound for the development of new, safe, and green pesticides (Wu *et al.* 2012a). The antifungal activities of compounds **27b–e** (Fig. 3) against *Botrytis cinerea* of 75, 67, 75, and 62%, respectively, are superior to that of the lead compound **27a**. The insecticidal activity of compound **27f** (Fig. 3) against *P. xylostella* was 100% at 200 mg L^{-1}, which was higher than those of the control Thiamethoxam and lead compound **27a**. The antifungal activity is enhanced by larger groups on the amide; thus, the introduction of phenyl groups leads to greater activities than the incorporation of methyl or H substituents (Wu *et al.* 2012b).

Dihalopropene ether containing a piperazine carbamate showed high insecticidal activity against the adult, larval, and egg forms of harmful insects in the agricultural, civil, and animal husbandry sectors. The lethality of compound **28b** (Fig. 4) against *P. xylostella* larvae was greater than 50%, and the lethality of compound **28a** (Fig. 4) against 2nd instar larvae of *P. xylostella* was 90% at 6.25 mg L^{-1} (Liu *et al.* 2012). The insecticidal activity of piperazine derivative **28c**, which contains a dichloropropene ether (Fig. 4), against *P. xylostella* was 90% at 6.25 mg L^{-1}, which is higher than that of the control, Pyridalyl (Yang *et al.* 2014). Pyridyl piperazine derivatives based on the classic serotonin receptor ligand have good insecticidal activity. The insecticidal activity of compound **29a** (Fig. 4) against nematode *Meloidogyne incognita* (Kofold & White) Chitwood is 99%. The inhibition rate of compound **29b** (Fig. 4) against rice planthopper is 100%, while those of compounds **29c** and **29d** (Fig. 4) against armyworm (*Mythimna separata*) are 80%; and compounds **29d–g** (Fig. 4) exhibit 100% inhibition rates against *Aphis medicagini*. The introduction of Cl and CF_3 groups at the pyridine ring connected to the NH of piperazine may improve the insecticidal activity (Shen *et al.* 2014). Many commercially available products for controlling invertebrate pests are used alone or in combination, and the formulation of more economical and safe compositions for controlling pests is an urgent issue that needs to be addressed. Compositions of the *N*-alkylated phthalimide piperazine derivatives **30** and **31** (Fig. 4) have good insecticidal activity against *Nilaparvata lugens*, *Tetranychus cinnabarinus*, *P. xylostella*, *Myzus persicae*, *Anopheles* mosquitoes and grubs (Mei *et al.* 2014).

Compound **32** (Fig. 4) exhibits excellent insecticidal activity toward *Aphis craccivora*, with an LC_{50} of 0.12 mmol L^{-1}. The use of molecular docking to study the binding mode of **32** and the nicotinic acetylcholine receptor (nAChR) showed that the ability to form hydrogen bonds coupled with the molecular shape and size has a great influence on the insecticidal activity. That study increased our

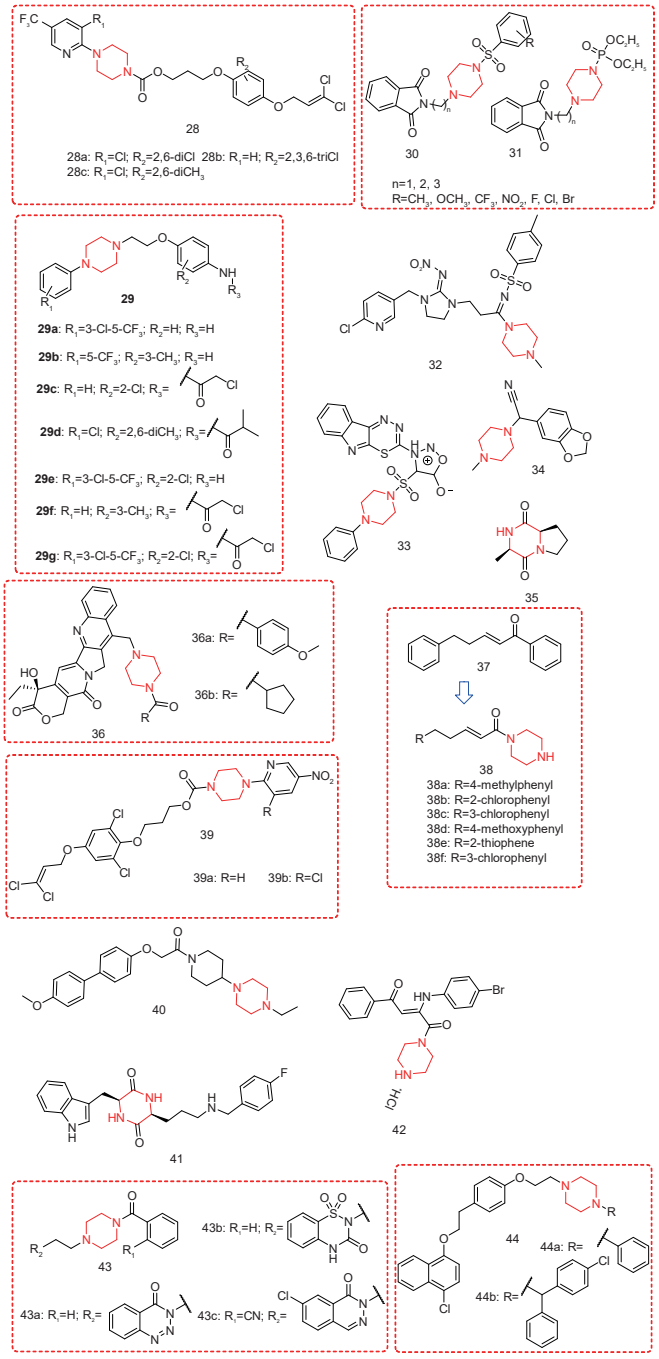


Fig. 4 Piperazine derivatives (28–44) with insecticidal activity.

understanding of the mechanism and interaction between compound **32** and nAChR and provided guidance for further structural modifications (Wang *et al.* 2014). Compared with Cypermethrin, the mesoionic compound **33** (Fig. 4) has some insecticidal activity against the *P. americana*, but it is not greater than Cypermethrin. SAR analysis showed that when piperazine is replaced with morpholine, the insecticidal activity improves significantly (Dubey *et al.* 2014). Compound **34** (Fig. 4) exhibits insecticidal activity against *A. aegypti* larvae, and its IC_{50} value against third-instar larvae is 275.3 μmol L^{-1}. Replacing methylpiperazine with morpholine or pyrrolidine significantly improves the insecticidal activity (Carreño Otero *et al.* 2014). The LC_{50} values of piperazinone derivative **35** (Fig. 4) against *Bursaphelenchus xylophilus* and *Ditylenchus destructor* are 451.3 and 366.6 mg L^{-1}, respectively, at 72 h (Zeng *et al.* 2015). The 7-(1-acylpiperazin-4-yl) methylcamptothecin derivatives **36a** and **36b** (Fig. 4) have good insecticidal activity against *T. cinnabarinus*, with LC_{50} values of 8.10 and 9.05 mg L^{-1}, respectively, at 24 h; while the LC_{50} values for *B. xylophilus* are 6.34 and 6.68 mg L^{-1}, respectively. Since camptothecin has a rigid framework and low solubility, the introduction of an amide structure increases the solubility and improves the insecticidal activity. The insecticidal activity of the target compound is higher than that of camptothecin (Li *et al.* 2015).

The concentration for the 50% of maximal effect (EC_{50}) values of compounds **38a–c** (Fig. 4) against *Pythium aphanidermatum* are 0.14, 0.10, and 0.075 mmol L^{-1}, respectively, which are better than that of the lead compound **37** (Fig. 4). The best insecticidal activities are for compounds **38d–f** (Fig. 4), and the lethal rates of these three compounds against mosquito (*C. pipiens pallens*) are 100% at 1 mg L^{-1}. Preliminary SAR analysis shows that the methyl group influences the activity of the synthesized compounds (Xu *et al.* 2016). Dihalopropylene ether compounds have high insecticidal and bactericidal activities against *P. xylostella* and *M. separata*. The biological activity test results against *M. separata* showed that compounds **39a** and **39b** (Fig. 4) have insecticidal activities greater than or equal to 90% at 20 mg L^{-1}, which is comparable to that of the control pesticide Pyridalyl. The insecticidal activities of these compounds against armyworm were 90 and 80% at 10 mg L^{-1}. The bactericidal activity test results indicated that the activities of compounds **39a** and **39b** against *Sclerotonia sclerotiorum* were 90–100% at 25 mg L^{-1}; against *Erisiphe griminis* the compounds exhibited inhibition rates of 70% at 500 mg L^{-1}, and a 75% inhibition rate at 500 mg L^{-1} was reported against corn rust (Liu *et al.* 2017). Compound **40** (Fig. 4) has good inhibitory activity against the three enzymes of mosquito acetylcholinesterase 1 (AChE1), with IC_{50} values against *Aa*AChE1, *Ag*AChE1, and G122S-*Ag*AChE1 of 0.23, 0.40, and 0.96 μmol L^{-1}, respectively. The activity declined significantly when the piperidine in compound **40** was replaced with ethylpiperazine or morpholine, whereas changing the ethyl group on the piperazine to methyl had little effect. Replacing the piperazine ring with piperidine or morpholine rings and replacing piperidine with a propyl group led to significant reductions in activity. After changing 4′-methoxybiphenyl to 4-iodophenyl, the activity was also significantly reduced (Knutsson *et al.* 2018).

Structural optimization of piperazine dione derivatives led to the identification of target compound **41** (Fig. 4) as the most active compound against *Meloidogyne incognita*, with nematicidal activity of 75% at 2.4 μmol L^{-1}. The insecticidal activity improved when electron-withdrawing substituents were introduced on the benzene ring (e.g., the introduction of F in the 4-position of the phenyl group for compound **41**). The length of the chain also influences the activity. Whereas good insecticidal activity is observed with a propyl group as the intermediate chain, the activity is reduced when the chain length is shortened (Sun *et al.* 2018). The piperazine derivative 2-(4-bromophenylamino)-1-(piperazin-1-yl)-4-phenylbut-2-ene-1,4-dione hydrochloride (**42**, Fig. 4) exhibits excellent insecticidal activity and low toxicity (Pulina *et al.* 2018). At 40 mg L^{-1}, compounds **43a–c** (Fig. 4) have significant nematicidal activity against *M. incognita*, with disease indexes of 0.3, 0.2 and 0.2, respectively (Xu *et al.* 2018). Disubstituted benzene compounds containing the piperazine structure **44a**, **44b** (Fig. 4**)**, and **45** (Fig. 5**)** are mainly used to control resistant pests such as mosquitoes and cockroaches (Velten *et al.* 2018). Compounds **46a** and **46b** (Fig. 5) have good insecticidal activity against *M. separata* Walker, with mortality rates of 75 and 80%, respectively, at 200 mg L^{-1} (Zhang *et al.* 2018a). Compounds **47a–c** (Fig. 5) have good antibacterial activities that are higher than those of the control drugs metalaxyl and diacetylene amide, and they have significant insecticidal activity against *A. gossypii*, *Plutella xylostella*, and *H. virescens*; and these compounds also exhibit selective weed-killing of Zinnia, velvetleaf, green foxtail, and barnyard grass. They not only have good molecular solubility but also good insecticidal and bactericidal activities (Shao *et al.* 2018).

The insecticidal activities of fluorine-containing pyridine piperazine derivative **48a** (Fig. 5) against *P. xylostella* and *S. exigua* are 96.7 and 84.5%, respectively, at 5 mg L^{-1}, which are higher than those of acetamiprid (94.4 and 82.2%, respectively). The introduction of a pyrazole ring can enhance insecticidal activity. Replacing the pyrazole ring with a *p-tert*-butylphenyl group reduces the activity. Derivatives bearing single-chain *n*-butyl and *n*-propyl esters are superior to those containing a *sec*-butyl ester or other aromatic hydrocarbon groups (Peng and Wang 2018). At 100 mg L^{-1}, the fluorine-containing pyridyl compounds **48b–d** (Fig. 5) have excellent insecticidal activity against *P. xylostella*, with inhibition rates of 100%; while the insecticidal activities are 90, 80, and 60%, respectively, at 10 mg L^{-1}, and 69, 55, and 38%, respectively, at 1 mg L^{-1} (Wang *et al.* 2019). At 20 mg L^{-1}, a series of 1,2,3-benzotriazin-4-one derivatives with piperazine as the linking group have good insecticidal activity against *M. incognita*; especially compound **49** (Fig. 5) with an inhibition rate of 71.4%, indicating that the piperazine derivatives have an inhibitory effect on *M. incognita*. SAR analysis showed that the position and type of the substituent have a greater influence on the activity. The introduction of halogen (Cl), electron-donor (CH_3, OCH_3), or electron-withdrawing (OCF_3, NO_2) groups increase the activity. Thus, compound **49** has potential biological activity and is worthy of further study (Chen *et al.* 2019). Compounds **50a**–**c** (Fig. 5),

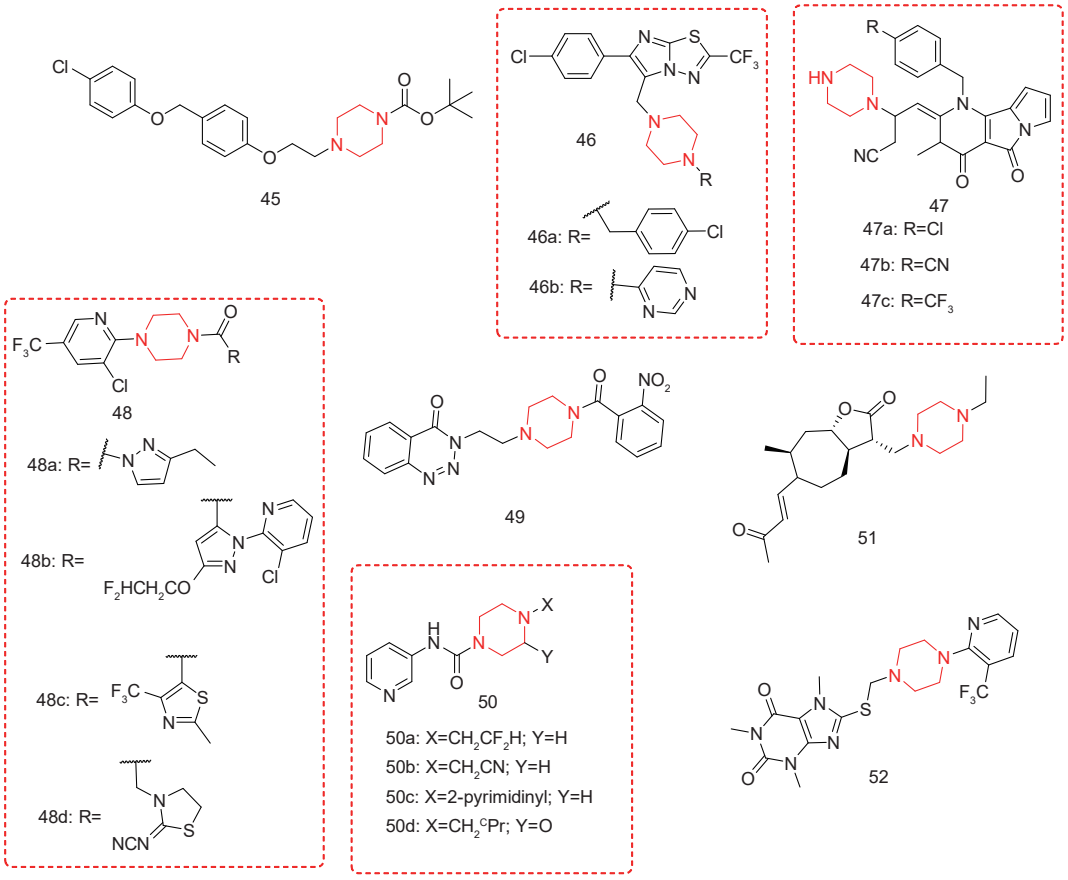


Fig. 5 Piperazine derivatives (45–52) with insecticidal activity.

which are 3-aminopyridine urea derivatives containing a piperazine ring, have significant insecticidal activity against *M. persicae* at 200 mg L^{-1}. In these compounds, the distal nitrogen of the pyrazine contains an electron-withdrawing group. The 2-ketopiperazine analogue **50d** (Fig. 5) also has significant insecticidal activity against *M. persicae*. This indicates that since the electron-withdrawing substituent on the piperazine nitrogen reduces the basicity of the molecule, the presence of a basic nitrogen atom in this region is unfavorable. This series of compounds has little activity against *Bemisia tabaci* (Lambert *et al.* 2020). The insecticidal and egg-killing activities of compound **51** (Fig. 5) against *P. xylostella* larvae (72 h) and eggs are 33.3 and 41.7% at 20 and 10 mg L^{-1}, respectively. The introduction of an amino or thiol group at the position where xanthine is connected to the piperazine enhances the antifungal and egg-killing activities. In addition, the extracellular double bond has a significant influence on larvicidal activity (Zhi *et al.* 2020). Piperazine-substituted purine derivative **52** (Fig. 5) is superior to Triflumuron against *P. xylostella* (90% *vs.* 37% for Triflumuron at 10 mg L^{-1}). The presence of CF_3 in the structure is conducive to its insecticidal activity (Fan *et al.* 2025).

2.2. Antiviral activity

Viral plant diseases are a major cause of economic losses in agricultural production. In recent years, economic development has led to an increasing focus on issues that affect quality of life, health, and the environment, which has led to more stringent requirements and safeguards for the use of pesticides. Currently, Ningnanmycin and Ribavirin are the most widely used anti-plant-virus agents. However, because Ningnanmycin is easily decomposed by light, its field control effect is low, and Ribavirin offers low control efficiency. Therefore, there is an urgent need to develop antiviral agents with high efficiency, low toxicity, safety to non-target organisms and environmental friendliness. Piperazine is an important nitrogen-containing heterocycle, and its amide and sulfonamide derivatives have been widely used in antiviral activity studies. Compounds **53a** and **53b** (Fig. 6) exhibit good inhibitory activities against *tobacco mosaic virus* (TMV). The protective, curative, and inactivating activities against TMV of compound **53a** are 58.7, 57.3, and 85.7%, respectively, whereas those of **53b** are 58.3, 56.3 and 85.9%, respectively. These activities are comparable to those of Ningnanmycin (59.6, 57.3, and 88.5%, respectively). The introduction of 4-NO_2 and 3-Br on the benzene ring enhances the antiviral activity, whereas the introduction of 4-F, 4-NO_2, 3-Br, and 2,4-di-Cl enhances the antibacterial activity (Reddy *et al.* 2013). Both *in vivo* and *in vitro* tests on phenanthrene-containing *N*-heterocyclic derivatives **54** and **55** (Fig. 6) revealed that their anti-TMV activities are comparable to those of Ribavirin. The *in vitro* activity of **54** against TMV is 32% at 500 mg L^{-1}, and its curative, protective, and inactivating activities *in vivo* are 33, 36, and 40%,

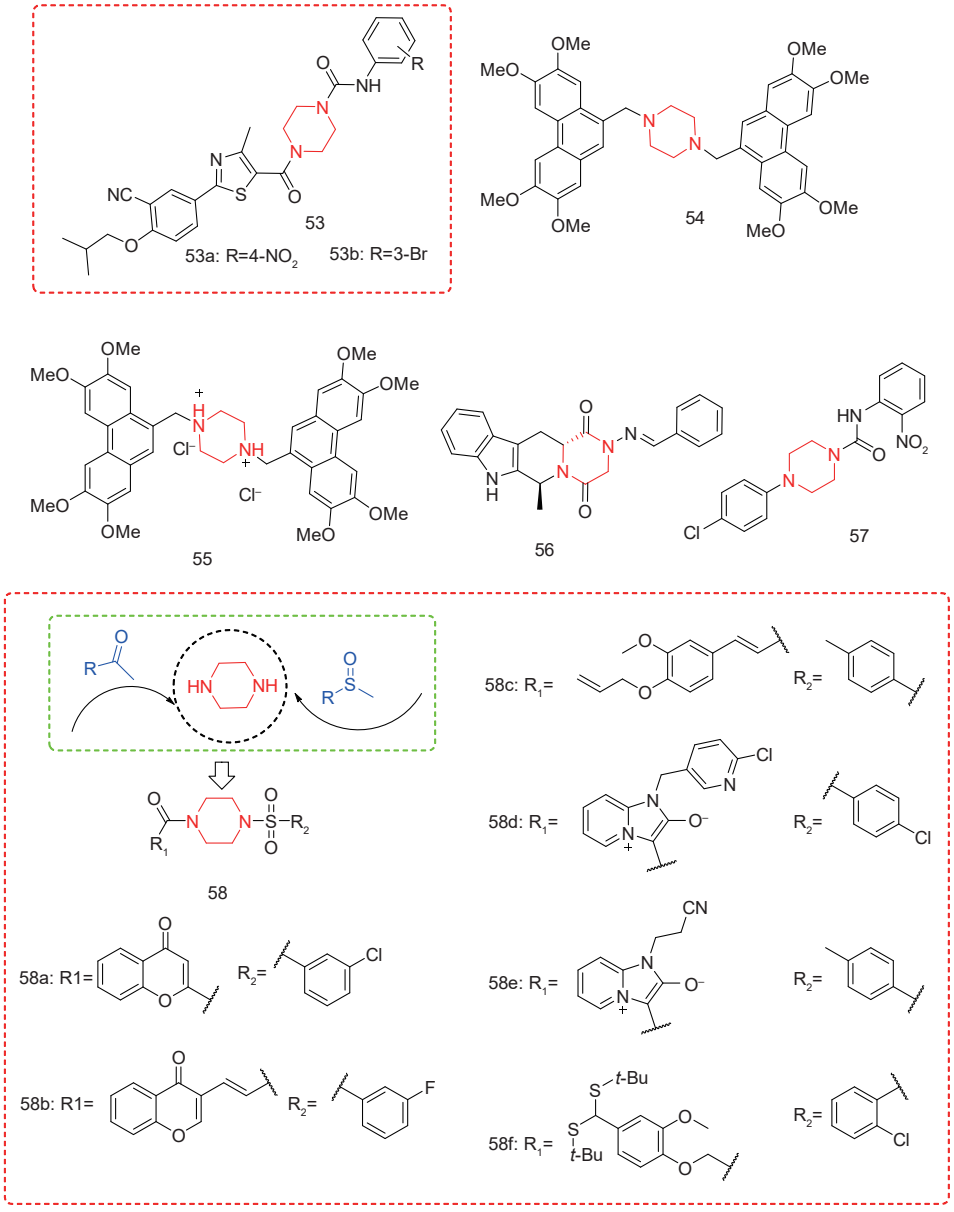


Fig. 6 Piperazine derivatives (53–58) with antiviral activity.

respectively. The *in vitro* inhibition rate of **55** against TMV is 45%, and the inactivating, curative, and protective activities *in vivo* are 42, 40, and 35%, respectively. In comparison, the *in vitro* inhibition rate of Ribavirin against TMV is 40%, and the curative, protective, and inactivating activities *in vivo* are 36, 38, and 35%, respectively. These results show that the hydrochloride form of piperazine has enhanced antiviral activity (Yu *et al.* 2015).

Based on inhibition of the TMV coat protein (CP) assembly, the *in vitro* and *in vivo* inactivating, curative and protective activities of compound **56** (Fig. 6) against TMV are 52, 49, 50, and 52% at 500 mg L^{-1}, respectively. These levels are superior to those of other diastereoisomeric compounds, indicating that the spatial configuration affects the antiviral activity (Xie *et al.* 2020). Compound **57** (Fig. 6) has high affinities with TMV-helicase and TMV-CP, and the interactions between TMV-CP and small molecules can weaken the interaction between TMV-CP subunits and lead to the inability of TMV particles to self-assemble (Nagalakshmamma *et al.* 2020). Jiang *et al.* (2021a) discovered that compound **58a** (Fig. 6) exhibits anti-*tomato spotted wilt virus* (TSWV) activity. Later, they reported that compound **58b** (Fig. 6), which was optimized by three-dimensional quantitative structure–activity relationship (3D QSAR) studies, exhibited improved anti-*tomato chlorosis virus* (ToCV) activity. The binding force between compound **58b** and ToCVCP is 0.11 μmol L^{-1} as revealed by *in vitro* microscale thermophoresis. Real-time quantitative polymerase chain reaction (RT-qPCR) showed that **58b** can significantly reduce the content of the *ToCVCP* gene *in vivo* (Jiang *et al.* 2021b). Yuan *et al.* (2022) revealed that compound **58c** (Fig. 6) exhibits higher activity against TMV and *cucumber mosaic virus* (CMV) than Ningnanmycin. Piperazine derivatives show anti-PVY activity with the introduction of mediating ions, and compound **58d**

(Fig. 6) shows higher activity against PVY than Ningnanmycin (Li *et al*. 2022). The protective activity of piperazine derivative **58e** (Fig. 6) against TSWV is superior to that of Ningnanmycin. Proteomic and defensive enzyme activity results showed that **58e** inhibits TSWV infection by regulating tobacco defensive enzyme activity and inducing the oxidative phosphorylation pathway (Zhang W B *et al*. 2024). Wang *et al*. (2025) reported that dithioacetal piperazine derivatives have good activity against TSWV and that compound **58f** (Fig. 6) interacts with the TSWV nuclear capsid protein (NP) through hydrogen bonding.

The activity of the 1,3,4-oxadiazole derivative **59** (Fig. 7), which has a piperazine ring, against TMV is higher than that of Ningnanmycin. Transmission electron microscopy (TEM) studies showed that the mechanism through which **59** acts against TMV involves the destruction of TMV particle assemblies. In addition, after treatment with **59** of the green fluorescent protein (GFP)-labelled TMV-infected clone (TMV-GFP), observations under UV lamp irradiation, Western blot analysis, and RT-qPCR detection showed that the fluorescence intensity of GFP, the content of GFP protein, and the gene content were significantly lower than those of the control. These results indicated that **59** reduces the proliferation of TMV (Ji *et al*. 2022). In addition, the reported activity of compound **60a** (Fig. 7) against CMV and TMV was superior to that of Ningnanmycin. Defensive enzyme activity tests and preliminary proteomic mechanism studies showed that compound **60a** increases the activity of various defensive enzymes and enhances the phenylpropane biosynthetic pathway in tobacco to improve its anti-TMV activity (Zhang *et al*. 2022). Compound **60b** (Fig. 7) exerts antiviral activity through a strong binding interaction with CMV CP, which affects the self-assembly of CMV (Zhang *et al*. 2023). Compound **61** (Fig. 7) shows some anti-TMV activity and may affect TMV assembly by binding to TMV CP, thus affecting viral replication (Zhang G L *et al*. 2024). Compound **62** (Fig. 7), derived from 3D-QSAR, showed good activity against PVY. Molecular docking showed that **62** can form a hydrogen-bond interaction with Glu150, a key amino acid in the PVY CP (Bai *et al*. 2023). Li *et al*. (2023) reported that piperazine derivatives have anti-TSWV activity, and the activities of compounds **63a** and **63b** (Fig. 7) may be related

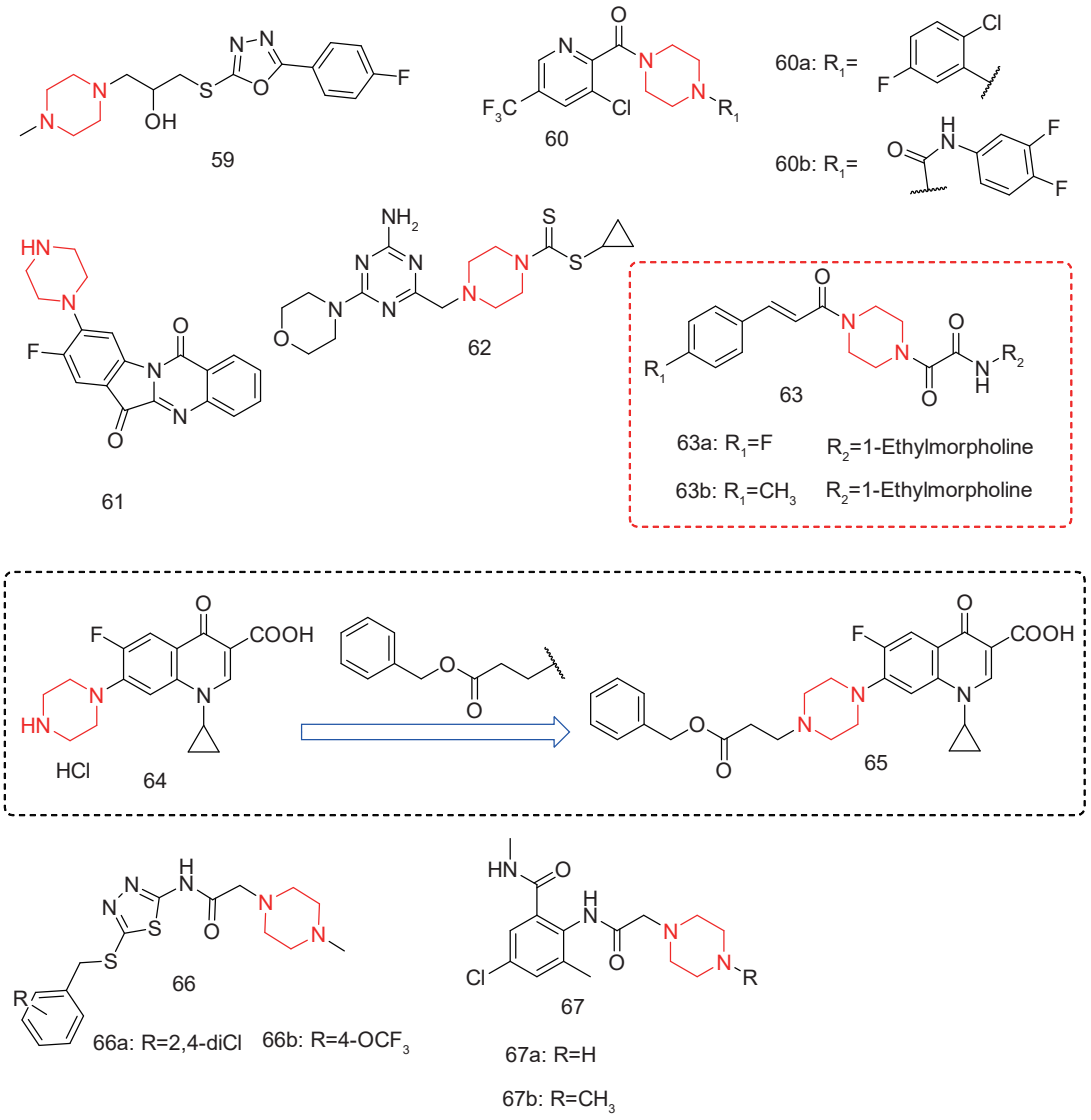


Fig. 7 Piperazine derivatives (59–63) with antiviral activity.

to the binding of amino acid Arg94 on the NP of TSWV, which interferes with ribonucleoprotein (RNP) assembly and reduces the proliferation of TSWV.

2.3. Antibacterial activity

The last several years have seen significant advances in the development of piperazine derivatives as antibacterial agents, and strong antibacterial activity has been achieved. The application of 0.025% of compound **64** (Fig. 8) gave 80% protection against *Xanthomonas oryzae* on rice plants (Grohe *et al*. 1984). Compound **65** (Fig. 8) gave 50% protective effects against *X. oryzae* at 10 mg per 100 cm (Petersen *et al.* 1984). Heterocyclic amide compounds can impart extensive biological activities and are widely introduced in the design of pesticides. For example, 1,3,4-thiadiazole amides can promote plant growth and have anticancer, anti-inflammatory, antiviral, herbicidal, insecticidal, and antibacterial activities. Compounds **66a** and **66b** (Fig. 8) impart better resistance to *X. oryzae* and exert inhibitory activity against *Ralstonia solanacearum* (*Rs*). The EC_{50} values of **66a** and **66b** against *X. oryzae* are 17.5 and 19.8 mg L^{-1}, respectively, which are better than that of the control compound Bismerthlazol (Xue *et al.* 2014). The antibacterial activity of compound **67a** (Fig. 8) against *X. oryzae* pv. *Oryzae* (*Xoo*), *Xanthomonas axonopodis* pv. *Citri* (*Xac*), and *Rs* are 47, 47, and 51% at 200 mg L^{-1}, respectively. The inhibition rates of compound **67b** (Fig. 8) against *Rs*, *Xac*, and *Xoo* are 41, 53, and 40%, respectively, at the same concentration. Introducing water-soluble groups can improve solubility and thus increase the antibacterial activity (Zhou *et al.* 2016). The inhibition rates of compounds **68a** and **68b** (Fig. 8) for *Xoo* are 94 and 100%, respectively, at 200 mg L^{-1}. The inhibition rates against *Xac* are 98 and 99%, respectively, which are higher than that of the control thiediazole copper (at 34 and 45%, respectively). At the same time, some compounds have shown antifungal activity against *Gibberella zeae*, *Fusarium oxysporum*, *Phytophthora infestans*, *Pellicularia sasakii*, *Colletotrichum capsici*, and *Gleosporium fructigenum* at 50 mg L^{-1}. The introduction of phenyl and Boc groups on the piperazine ring enhance the antibacterial activity, whereas the antibacterial activity decreases with ethyl and methyl substituents. In addition, the introduction of a symmetric structure on the two NH groups of the piperazine ring increases the antibacterial activity (Yan *et al.* 2016).

Compounds **69a** and **69b** (Fig. 8) exhibit excellent antibacterial activities against *Rs* and *Xoo*, with EC_{50} values of 2.7 and 8.5 mg L^{-1}, respectively, for *Rs*. 3D QSAR studies were conducted on these compounds to guide their further structural optimization. When scanning electron microscopy (SEM) was used to monitor the shape of *Rs* upon exposure to **69a**, bacterial breakage and fragmentation were observed, indicating that **69a** has a strong interaction with *Rs*. Comparative molecular field analysis (CoMFA) showed that the introduction of an appropriately sized group near the 4-position of the benzene ring enhances the antibacterial activity, but the introduction of larger groups, such as methyl and methoxy groups, reduces the activity. For example, when Br, Cl, and F are introduced at the 4-position the activity is greater than when methyl and methoxy groups are

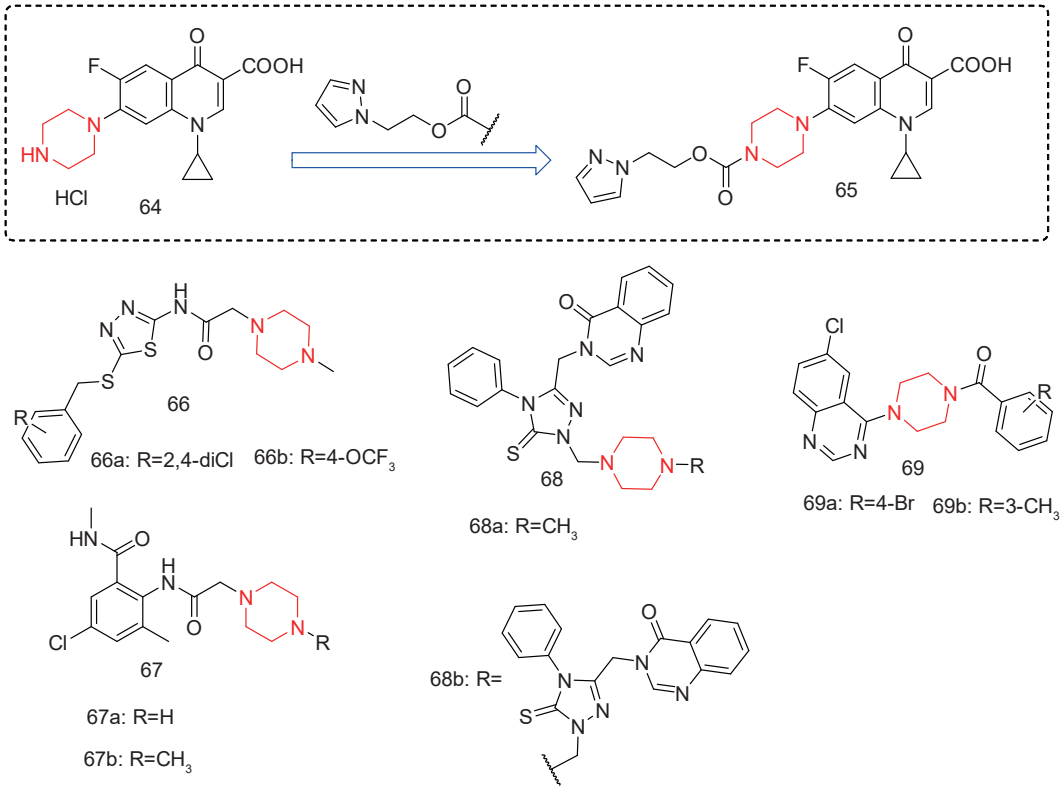


Fig. 8 Piperazine derivatives (64–69) with antibacterial activity.

introduced, and the activity of the derivative with F and Br at the 2- and 4-positions, respectively, is greater than that of the derivative with F at both of these positions simultaneously. At the same time, when a larger substituent is introduced at the 2-position of the benzene ring the activity is greater than when a smaller substituent is introduced. For example, when substituents are introduced at the 2-position, the activity decreases in the order of 2-CH_3>2-OH>2-Br, 4-F>2, 4-di-F, 2-CH_3>2-Cl. In addition, the antibacterial activities of compounds with electron-donating groups (2-CH_3 and 2-OH) introduced on the benzene ring are higher than those of compounds substituted with electron-withdrawing groups (2-Br, 4-F, 2-Cl, and 4-Br) (Shao *et al.* 2020).

The 1,4-benzoxazin-3-one propanolamine derivatives possess excellent antibacterial activity. In particular, the *in vitro* EC_{50} values of compound **70** (Fig. 9) against *Xoo*, *Pseudomonas syringae* pv. *actinidiae* (*Psa*), and *Xac* are 8.5, 5.0, and 4.7 mg L^{-1}, respectively. The curative and protective activities of **70** *in vivo* against rice bacterial leaf blight are 51.1 and 48.2%, respectively. The activities of compound **70** both *in vivo* and *in vitro* against the tested bacteria are higher than those of the control compounds thiodiazole copper and Bismerthiazol. The introduction of aromatic substituents on the NH of piperazine enhances the antibacterial activity whereas alkyl groups reduce the activity. Introducing electron-withdrawing groups on the aromatic rings increases the antibacterial activity more than the introduction of electron-donating groups; however, introducing two electron-withdrawing groups reduces the activity. The introduction of a carbazole ring into compound **70** gives higher antibacterial activity than when aromatic rings are included, indicating that carbazole is crucial for antibacterial activity. SEM observations revealed that compound **70** damages the cell walls of *Xoo* cells and causes them to break, thus exhibiting antibacterial activity. Its mechanism of action is through cell lysis and death (Rao *et al.* 2020).

Cell inducers can effectively regulate the physiological and pathological processes of cells and induce the apoptosis

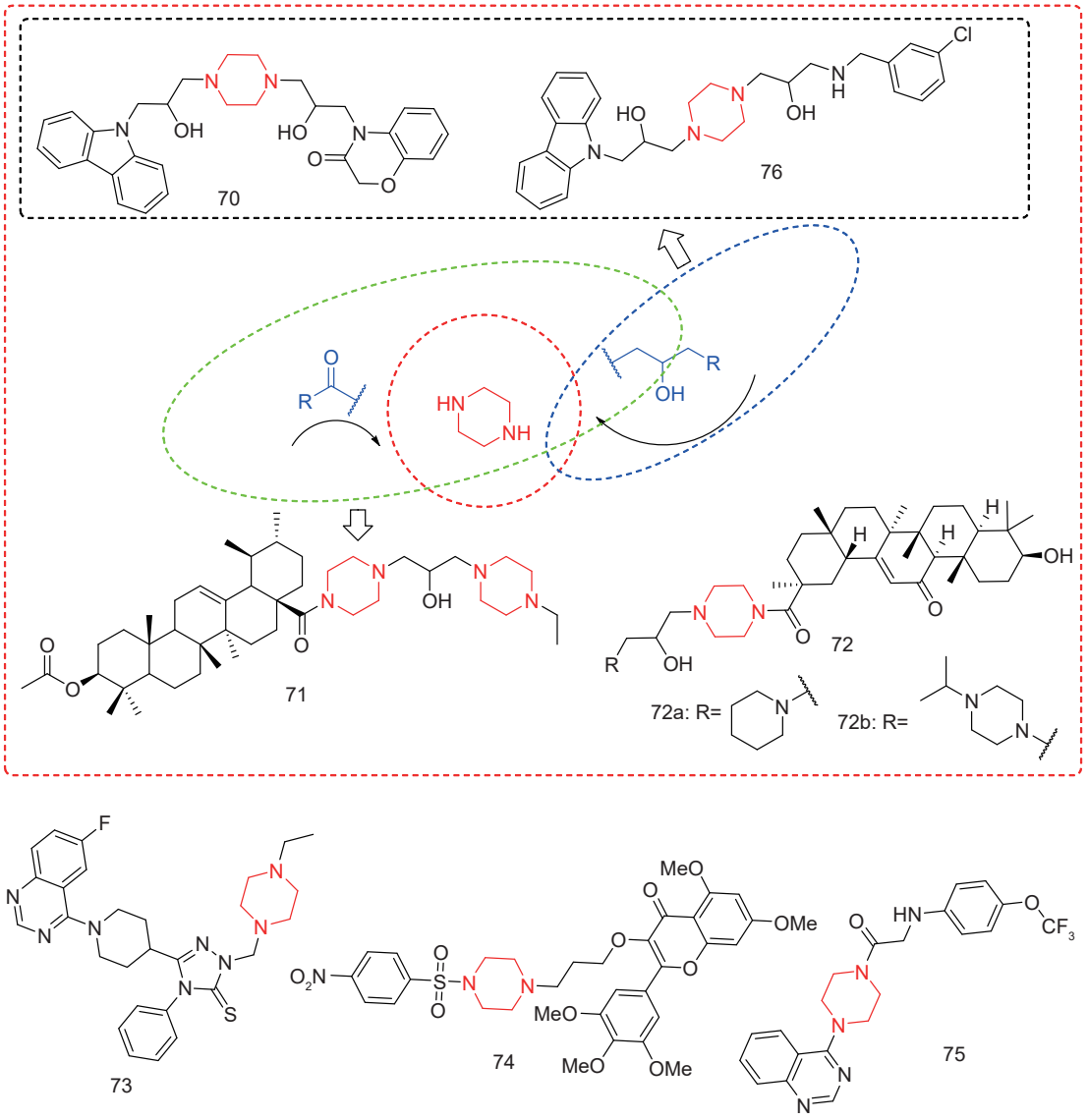


Fig. 9 Piperazine derivatives (70–76) with antibacterial activity.

of unfavorable cells. The antibacterial activity of **71** (Fig. 9) against *Xac* and *Xoo* is superior to that of thiodiazole copper. In addition, **71** can be used to treat bacterial blight *in vivo*. Compound **71** causes reactive oxygen species (ROS) accumulation by reducing the activities of the defensive enzymes superoxide dismutase and catalase (Wang *et al.* 2020). Piperazine rings were introduced into 18b-glycyrrhetinic to obtain **72a** and **72b** (Fig. 9), which has anti-*Xac* and *Xoo* activities. Treatment with **72a** and **72b** induces ROS accumulation in *Xac* and *Xoo*, and leads to morphological deformation of the pathogen, eventually leading to apoptosis (Xiang *et al.* 2020). Good *in vitro* and *in vivo* activities were observed for compound **73** (Fig. 9) against *Xoo*. In particular, *in vitro* studies showed that **73** exhibits an approximately five times higher inhibitory effect on *Xoo* than cuculazole. SAR analysis showed that the anti-*Xoo* activities of piperazine compounds with weakly electron-donating groups are better than those with electron-withdrawing groups. SEM observations of the morphology of *Xoo* upon exposure to **73** indicate that leakage of the bacterial contents into the extracellular environment may occur, presumably through changes in membrane permeability (Shi *et al.* 2020). The activities of compound **74** (Fig. 9) against *Rs*, *Xac*, and *Xoo* are superior to those of the control drug. Treatment of the bacteria with compound **74** causes damage to their structure and integrity, thus inhibiting their growth (He *et al.* 2021). Compound **75** (Fig. 9) exhibits antibacterial activity against *X. oryzae* pv. *Oryzicola* (*Xoc*). This activity may be caused by changes to the bacterial morphology and permeability and by disruption of the exopolysaccharides and extracellular enzymes, which reduces the mobility of the bacteria and the motility of the flotilla (An *et al.* 2024). Compound **76** (Fig. 9) has better antibacterial activities against *Xoo*, *Psa*, and *Xac* than bismerthiazol and thiodiazole copper, and it also has antibacterial activity against rice bacterial leaf blight (Ma *et al.* 2024). Compound **77** (Fig. 10), obtained by introducing a piperazine ring into the aurone, shows good antibacterial activities against *Xoc*, *Xoo*, and *Xac*, and its inhibition of rice bacterial leaf streak *in vivo* is comparable to that of thiodiazole copper. The study showed that **77** activates the abscisic acid immune signalling pathway by increasing defensive enzyme activities and chlorophyll levels, and by up-regulating *OsABF1*, *OsBIPP2C1*, and *OsPYL/RCAR5*, which are related to the abscisic acid pathway (Wang *et al.* 2024). Compound **78** (Fig. 10) has good anti-*Xoo* and *Xac* activities (Zeng *et al.* 2024).

2.4. Antifungal activity

Research on the antifungal activity of piperazine derivatives has made some significant advances. For example, Triforine is a systemic fungicide with a piperazine framework that has attracted widespread interest from many researchers in recent years. At 40 mg L^{-1}, the inhibition rates of compounds **79a** and **79b** (Fig. 10) against brown leaf rust and barley mildew

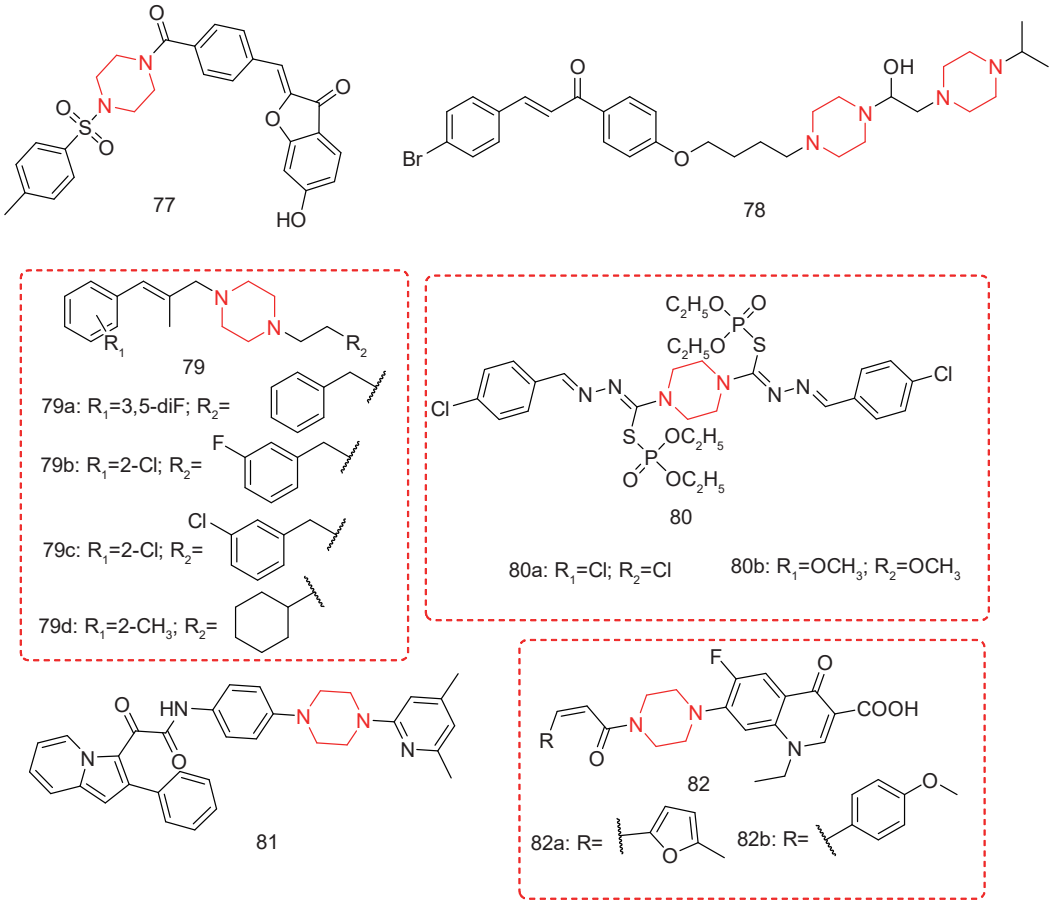


Fig. 10 Piperazine derivatives (77–78) with antibacterial activity and (79–82) with antifungal activity.

are almost 100%. The antifungal activities of **79c** and **79d** (Fig. 10) against *Cucumber Downy Mildew* are also almost 100% at 500 mg L^{-1} (Takashi *et al.* 1993). The inhibition rates of compounds **80a** and **80b** (Fig. 10) against *Colletotrichum falcatum*, *F. oxysporum*, and *Curvularia pallescence* are all 100% at 1,000 mg L^{-1} (Chandra *et al.* 2005). Compound **81** (Fig. 10) has a better inhibitory effect on *Fusarium solani*, with a MIC value of less than 1 mg L^{-1} (Downham *et al.* 2008). Compounds **82a** and **82b** (Fig. 10) have good antifungal activity against *Rhizoctonia solani* at 200 mg L^{-1}, with growth inhibition rates of 83 and 94%, respectively (Yu *et al.* 2009). The inhibition rates of compounds **83a** and **83b** (Fig. 11) against *Pseudoperonospora cubensis* are 91.2 and 84.5%, respectively. Based on the good antifungal activity of the synthesized compounds, additional compounds were constructed based on 3D QSAR studies. The results indicated that optimized compounds **83c** and **83d** (Fig. 11) have better activity against *P. cubensis*, with inhibition rates of 96.9 and 84.9%, respectively. The type and number of substituents on the benzene and pyrimidine rings influence the antifungal activities of the compounds. Introducing CH_3 groups at the 3- and 5-position of the pyrimidine ring and introducing a Cl moiety at the 4-position of the benzene ring increase the antifungal activity. Reduced activity is observed in the absence of a CH_3 group or when only one CH_3 group is introduced at the 3- or 5-position of the pyrimidine ring. An analysis with the CoMFA model showed that the introduction of large groups at the 2- and 3-position of the benzene ring results in reduced activity (Wang *et al.* 2010).

Compounds **83e** and **83f** (Fig. 11) have lower herbicidal activity against *Echinochloa crusgalli* and *Brassica campestris*, but they show excellent antifungal activity against the five fungi tested. The inhibition rates of compound **83e** against *Cercospora arachidicola* and *P. infestans* (Mont.) De Bary are 70.4 and 60.4%, respectively, at 50 mg L^{-1}. On the other hand, the inhibition rates of **83e** and **83f** against *F. oxysporum* f. sp. *Cucumerinum* are 80.4 and 82.6% at 50 mg L^{-1}, respectively, which are similar to that of the control Triadimefon (81.5%). The inhibition rate of **83e** against *Rhizogenesis* is 68.6% at 10 mg L^{-1}, which is also similar to that of the control Triadimefon (50.2%). When the benzyl ring attached to the 4-position of the piperazine ring is substituted with two Cl moieties, the antifungal activity of the compound is superior to those of the other compounds (Wang *et al.* 2011). Piperazine-containing benzofuroxan derivatives **84a** and **84b** (Fig. 11) have good activity against *Phytophthora capsica*, *Fusarium graminearum*, *S. sclerotiorum*, and *R. solani*, with EC_{50} values for **84a** of 9.07, 3.42, 2.52, and 3.40 mg L^{-1}, respectively, and 7.40, 4.52, 3.42 and 9.07 mg L^{-1}, respectively, for **84b** (Qiao *et al.* 2013). Benzofuran derivatives containing a piperazine structure have good antifungal activity against *Phytophthora capsici*, *F. graminearum*, *S. sclerotiorum*, and *R. solani*. Compounds **85a** and **85b** (Fig. 11) have the best activity against *F. graminearum* and *R. solani*, with IC_{50} values of 1.1 and 3.02 mg L^{-1}, respectively, which are approximately twice those

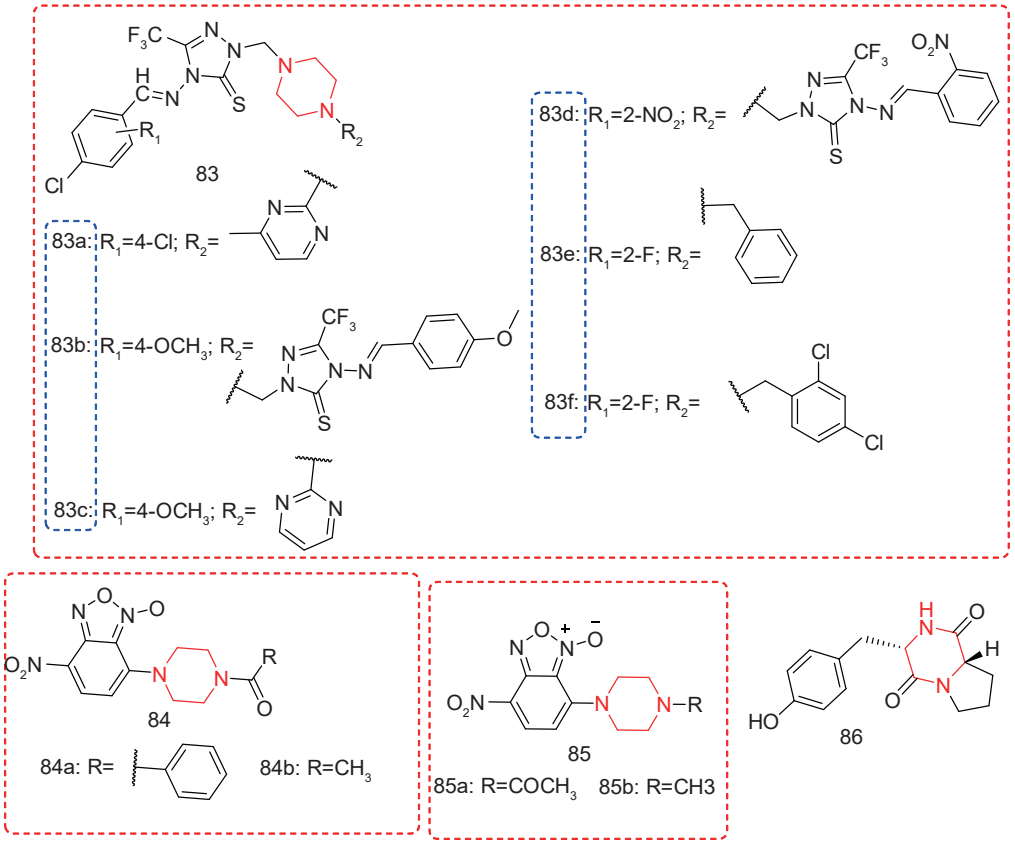


Fig. 11 Piperazine derivatives (83–86) with antifungal activity.

of the positive control carbendazim (which has IC_{50} values of 0.5 and 1.42 mg L^{-1}, respectively). Changing the substituent at the 2-position of the piperazine and introducing a 4-nitro group on the benzene ring generated candidates with good antifungal activity against *F. graminearum*. Replacing the nitro group on the benzene ring with a larger group, a sulfonyl group, or a strongly electron-withdrawing group, reduced the antifungal activity. Furthermore, compounds with more than two electron-withdrawing groups on the benzene ring also exhibit antifungal activity (Wang *et al.* 2013).

The development of microbial fungicides that can prevent and control fungal diseases caused by phytopathogenic oomycetes, such as grape downy mildew and late blight, is a focus of current fungicidal research. The low molecular weight 2,5-diketopiperazine ring derivative **86** (Fig. 11), with toxic activity against *Plasmopara viticola* and *P. infestans*, was isolated from the secondary metabolites of *Lysobacter capsici* AZ78. This compound can effectively kill their sporangia. Thus, the development of new low-toxicity 2,5-diketopiperazine ring derivatives is a promising avenue of research (Puopolo *et al.* 2014).

Compounds **87a–h** (Fig. 12) showed good antifungal activity against plant fungi both *in vivo* and *in vitro*, with inhibition rates exhibited by **87a–c** on *C. arachidicola* of 70.2, 70.4, and 70.3%, respectively, which were higher than that of the control Triadimefon (63.6%). The 80.0% inhibition rate exhibited by **87c** on *Fusarium oxysporum* was also better than that of the control Triadimefon (71.4%). Compounds **87e** and **87f** inhibited *Rhizobium cerealis* by 86.3 and 92.2%, respectively, showing good activity. Compounds of **87c** and **87d** inhibited *Pseudomonas syringae* pv. *Lachrymans* by 76.1 and 71.3%, respectively, which are higher than those of the control compounds Methylthiophenate (54.15%) and Methomycin (69.69%). The inhibition rates of compounds **87b**, **87c**, **87g**, and **87h** against *Ascochyta citrullina* Smith are 76.9, 73.7, 77.6, and 85.3%, respectively, which are higher than that of the control Validamycin (48.82%). The introduction of a CF_3 group on the triazole ring enhances the antifungal activity, and the introduction of a CH_3 group leads to a reduction in activity. When other substituents are unchanged, the introduction of a thiophene group increases the activity, and the introduction of a furan group reduces the activity. In most cases, the introduction of a CF_3 group increases the activity against *C. arachidicola* (Wang *et al.* 2015b). Mannich base compounds containing trifluoromethyl and piperazine groups exhibit herbicidal activity against rape and have good inhibitory activities *in vitro* against the rice ketol acid reductoisomerase (KARI) enzyme. These compounds also have good inhibitory activities *in vitro* against apple ring rot and wheat sheath blight. The herbicidal

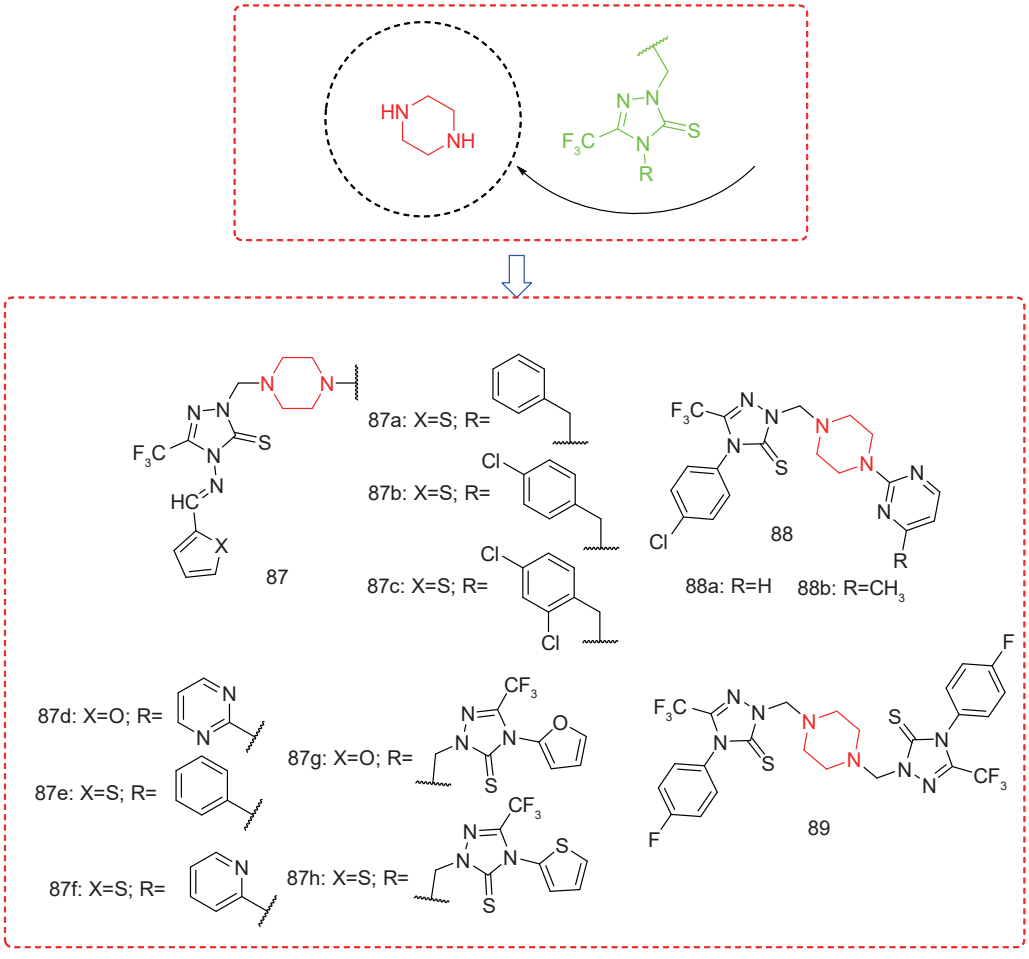


Fig. 12 Piperazine derivatives (87–89) with antifungal activity.

activities of **88a** and **88b** (Fig. 12) at 100 mg L^{-1} against rape are 67.9 and 74.5%, respectively. The inhibition rate of compound **89** (Fig. 12) against KARI is 86.1%. The bactericidal activities of compound **88a** against apple rot pathogen and *R. solani* are 65.2 and 77.0%, respectively. The bactericidal activities of compound **88b** against apple rot pathogen and *R. solani* are 54.3 and 78.4%, respectively (Wang *et al.* 2015a).

The inhibition rates of *S. sclerotiorum*, *P. capsici*, *F. graminearum*, *A. solani*, *P. infestans*, *R. solani*, and *B. cinerea* by compound **90** (Fig. 13) are 87.9, 63.0, 77.3, 66.7, 70.0, 70.0, and 80.0%, respectively, at 50 mg L^{-1} (Liu *et al.* 2015). The trifluorothione-containing triazolone compound **91** (Fig. 13) exhibits a wider range of antifungal activity, inhibiting *Rhizoctonia cerealis*, *Physalospora piricola*, *C. arachidicola*, *F. oxysporum*, *Gibberella sanbinetti*, and *A. solani* Sorauer at 89.3, 65.1, 70.0, 38.7, 68.3, and 42.1%, respectively. The antifungal activity is improved by introducing CF_3 on the triazolone ring, presumably because CF_3 endows the compound with high permeability and hydrophobicity. When CF_3 is introduced into the triazolazone, an aryl group substituted at the 4-position of the piperazine ring affects the antifungal activity; and while the introduction of a benzyl group increases the activity, the introduction of a 2,4-dichlorobenzyl moiety reduces the activity. The activities of the phenyl and pyridyl substituted compounds are similar, and the activity with a 4-CH_3 substituted pyrimidine is higher than that with 4,6-diCH_3 substituents. When CH_3 groups are introduced on the triazolethione, the introduction of a phenyl group on the 4-position of the piperazine ring increases the activity, whereas the introduction of a pyridyl causes a reduction in activity. The activity with 4-CH_3 substituted pyrimidine is the same as that with a CF_3 on the triazolethione; however, the activities of both are higher than that with 4,6-di-CH_3 substituents (Wang *et al.* 2015c).

Compound **92** (Fig. 13) exhibits antifungal activity against *Blumeria graminis*, *Phytophthora cactorum*, and *Fusarium culmorum*, with inhibition rates of 16.9, 36, and 42%, respectively. Good antifungal activity has also been reported against *R. solani* and *B. cinerea*, with inhibition rates of 73 and 75%, respectively (Zelechowski *et al.* 2015). At 20 mg L^{-1}, compound **93a** (Fig. 13) is effective against

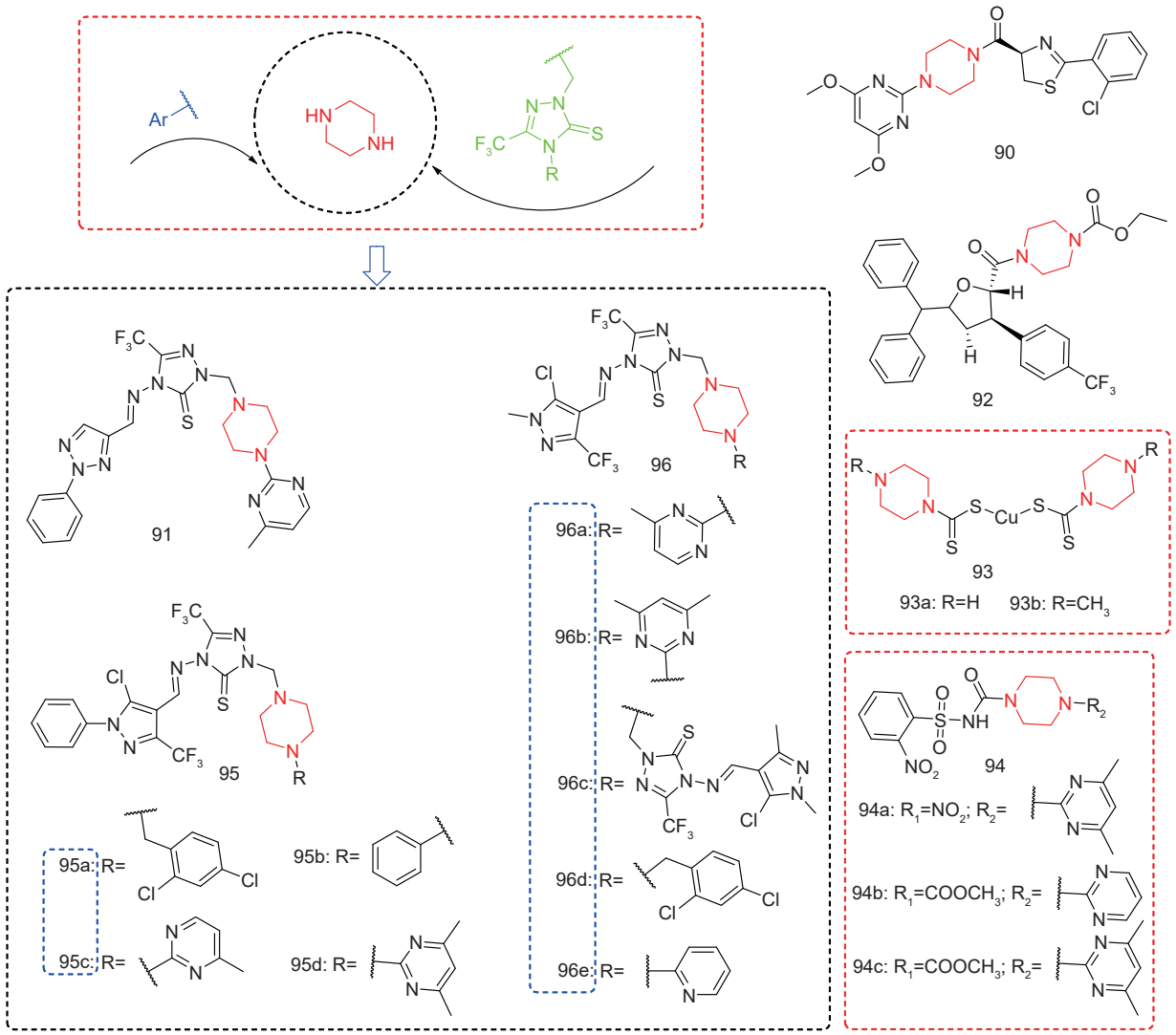


Fig. 13 Piperazine derivatives (90–96) with antifungal activity.

the pepper anthracnose, rice blast fungus, and apple tree rot pathogens, with inhibitory activities *in vitro* of 70.2, 71.2, and 100%, respectively. At 20 mg L^{-1}, compound **93b** (Fig. 13) exhibits inhibitory activities of 75.4, 77.3, and 100% against the pepper anthracnose, rice blast fungus, and apple tree rot pathogens, respectively. The *in vivo* inhibition rates of compound **93a** against wheat powdery mildew and cucumber powdery mildew at 100 mg L^{-1} are 77.5 and 77.4%, respectively, and its activities against apple tree rot and pear tree rot are both 100% at 2 g L^{-1}. The activity of compound **93b** against wheat powdery mildew and cucumber powdery mildew *in vivo* at 100 mg L^{-1} are 76.7 and 75.8%, respectively, and the *in vivo* inhibition rates against apple tree rot and pear tree rot at 2 g L^{-1} are both 100% (Wang Q M *et al.* 2016).

The piperazine and arylsulfonyl units are both present in carboxamide compounds that show good herbicidal activity on dicotyledons. Some of these compounds have good fungicidal activity. In particular, the fungicidal activities of **94a–c** (Fig. 13) of 90.4, 91.0, and 92.8%, respectively, against *Corynespora cassiicola*, are better than those of the control compounds methyl thiocyanate, isoproteron, and methomycin, and comparable to those of chlorthalidone and morphine. 3D QSAR studies have shown that the antifungal activity is enhanced by introducing an electron-withdrawing group on the 2-position of the benzene ring and introducing an electron-donating group on the 4- or 6-position of the pyrimidine ring. However, introducing large groups at the 2-position of the benzene ring reduces the antifungal activity (Wang B L *et al.* 2016a). Compounds **95a–d** (Fig. 13) exhibit herbicidal activity toward *Brassica napus* at 100 mg L^{-1} (with chlorsulfuron as a control). These compounds also showed higher and wider antifungal activity against *P. piricola*, *C. arachidicola*, *F. oxysporum*, *A. solani* Sorauer, *G. sanbinetti*, and *R. cerealis*, with activities comparable to that of the control triadimefon at 50 mg L^{-1}. Notably, introducing two CF_3 groups on the pyrazole and triazole rings improved the antifungal activity, whereas introducing only one CF_3 group or two CH_3 groups reduced the antifungal activity (Wang B L *et al.* 2016b).

Compounds **96a** and **96b** (Fig. 13) exhibit excellent antifungal activity *in vitro* against *P. piricola* and *R. cerealis*, and compound **96c** (Fig. 13) exhibits excellent antibacterial activity *in vitro* against *C. arachidicola* and *G. sanbinetti*. Compounds **96d** and **96e** (Fig. 13) have good antifungal activity *in vivo* against *Puccinia sorghi* Schw. The *in vitro* inhibition rate of compound **96d** against KARI is 87.5%, so it may be a promising KARI inhibitor. The CF_3 group on the triazole ring has a significant effect on the antifungal activity of the compounds, and replacing CF_3 with CH_3 results in reduced activity. When the substituent on the triazole ring is fixed, introducing a 2,4-dichlorobenzyl group on the piperazine ring leads to higher activity than that observed with a benzyl group. The introduction of 4-methylpyrimidine and 4,6-dimethylpyrimidine groups increase the antifungal activity, whereas the introduction of phenyl and pyridyl groups reduce the antifungal activity (Wang B L *et al.* 2016c).

Compounds **97a–c** (Fig. 14) show good inhibitory activities against apple rot pathogen at 50 mg L^{-1}, with inhibition rates of 53.1, 50.0, and 51.6%, respectively, which are similar to that of the control Triadimefon (53.1%). The inhibition rate exhibited by compound **97d** (Fig. 14) on KARI is 88.7%. Introducing an F substituent on the benzene ring increases the antifungal activity and replacing F with CF_3 reduces the antifungal activity (Zhang *et al.* 2016b). Compounds **98a**–**c** (Fig. 14) exhibit herbicidal activity against *B. campestris*, and show good antifungal activities *in vitro* against *G. sanbinetti*, *A. solani*, *R. cerealis*, *P. piricola*, *C. arachidicola*, and *F. oxysporum*. Compounds **98a–c** have good activity against rice KARI *in vitro*, with K_i values of 0.96, 3.86, and 3.10 μmol L^{-1}, respectively. These compounds may thus be used to study and develop new KARI inhibitors. Molecular docking and density functional theory (DFT) calculations show that the piperazine, furan, and oxadiazole rings in these compounds have a significant influence on the activity of KARI (Zhang *et al.* 2016a).

The inhibition of apple scab (*Venturia inaequalis*), *B. cinerea*, wheat acorn disease (*Blumeria graminis* f. sp. *tritici*), tomato blight (*P. infestans*), and wheat red rust (*Puccinia recondita*) by compound **99** (Fig. 14) are all above of 75% at 125 mg L^{-1} (Ihori *et al.* 2016). Compound **100a** (Fig. 14) exhibits inhibition rates of 85.1, 78.3, and 45.5% against *R. cerealis*, *P. piricola*, and *C. arachidicola*, respectively. In addition, compounds **100b–d** (Fig. 14) have good inhibitory activities against KARI *in vitro*, with K_i values of 0.38, 6.59, and 8.46 μmol L^{-1}, respectively; thus, these compounds may serve as leads for the development of KARI inhibitors. The introduction of large groups at the 3-, 4-, and 5-positions on the benzene ring connected to the 5-position of the triazole ring and the introduction of small groups on the piperazine ring improve the antifungal activity. The results of molecular docking studies indicated that the activity results from π–π interactions of the amino acid residues of KARI and compound **100b** (Wang *et al.* 2017). Phenazine-1-carboxylic acid is mainly used to control rice sheath blight, but it is harmless to humans, animals, and the environment, so it is an ideal compound for developing green pesticides. Phenazine-1-formylpiperazine derivatives **101a** and **101b** (Fig. 14) exhibit good antifungal activities against *Fusarium* wilt (*F. oxysporum* f. sp. *niveum*), rice sheath blight, tomato early blight, wheat scab (*Fusarium graminearum* Sehw.), and rice blast (*Pyricularia oryae* Cav.), with inhibition rates for **101a** of 69.8, 98.6, 85.3, 68.5, and 92.5%, respectively, and for **101b** of 98.2, 83.6, 68.3, 66.8, and 92.6%, respectively. These values are higher than those of lead the compound phenazine-1-carboxylic acid (PCA, Fig. 14) of 98.2, 73.3, 50.9, 47.9, and 86.1%, respectively (Wu *et al.* 2017).

Piperazine-containing 1,2,4-triazole Mannich base derivatives exhibit herbicidal activity against *B. campestris*, with some having antifungal activities against *R. cerealis*, *P. piricola*, and *F. oxysporum* that are better than those of the control compound, Triadimefon. The EC_{50} values of **102a–c** (Fig. 14) for *F. oxysporum* (9.5, 38.7, and 37.7 mg L^{-1}, respectively) and *P. piricola* (19.5, 15.5, and 13.8 mg L^{-1}, respectively) are better than those of the control, Triadimefon (47.90 and 36.5 mg L^{-1}, respectively). The introduction of Cl on the benzene ring increases the activity against *F. oxysporum*. The introduction of F on the benzene ring and

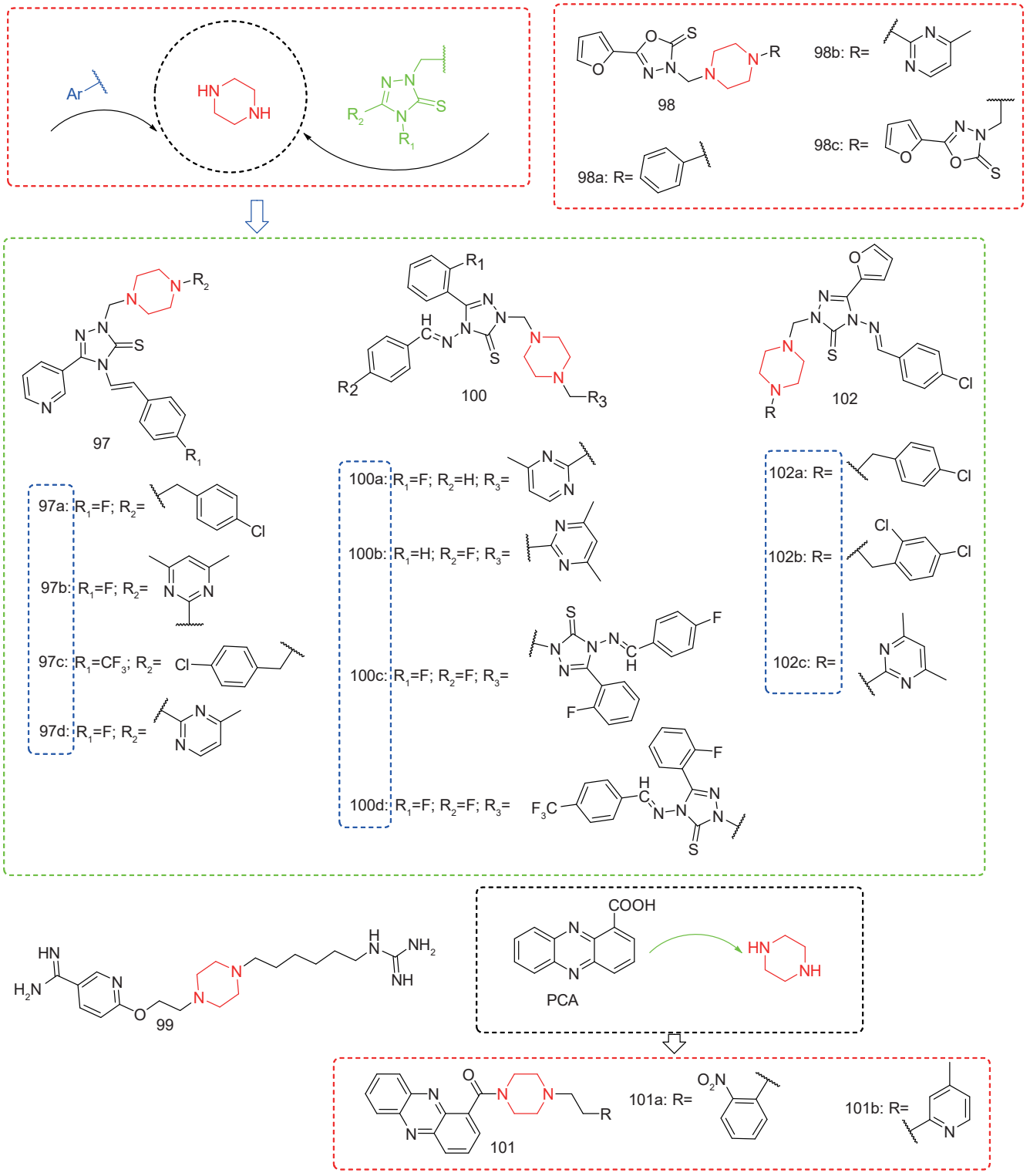


Fig. 14 Piperazine derivatives (97–102) with antifungal activity.

a dimethylpyrimidine group on the piperazine ring increase the activity against *C. arachidicola*. Introducing a CF_3 group into the compound usually leads to higher and broader antifungal activity. Generally, the introduction of Cl or CF_3 enhances the antifungal activity more than the introduction of F (Zhang *et al.* 2018b).

Bergenine derivatives containing piperazine have significant antifungal activities, and some compounds have higher antifungal activity than the control Azoxystrobin. The antifungal activities of compounds **103a–c** (Fig. 15) against *S. sclerotiorum* at 25 mg L^{-1} are 45.4, 56.3, and 49.2%, respectively, which are higher than that of the control, Azoxystrobin (42.08%). The antifungal activities of compounds **103a–c** against rice blast (*Pyricularia grisea*) at

100 mg L^{-1} are 40.4, 40.8, and 39.2%, respectively, which are comparable to that of the control, Azoxystrobin (38.75%) (Liu *et al.* 2018). Biological activity test results showed that the fluorine-containing pyridazine piperazine imidazole urea derivative **104** (Fig. 15) has good antifungal activities against tomato early blight (*P. infestans*), *F. oxysporum* (*C. cucumerinum*), peanut brown spot (*C. rachidicola*), *Botryosphaeria dothidea*, and *P. capsica* Leonian at 10 mg L^{-1}, with inhibition rates of 63.6, 65.5, 40.5, 64.0, and 63.5%, respectively (Wang *et al.* 2018c). The antifungal activities of piperazine-containing neopierophyllin derivatives **105a-d** (Fig. 15) against *V. inaequalis*, *B. cinerea*, (*B. graminis* f. sp. *Tritici*), *P. infestans*, and *P. recondita* are all higher than 75% at 125 mg L^{-1} (Ihori *et al.* 2018). Phenazine-1-carboxylic acid piperazine derivative **106** (Fig. 15) has excellent inhibitory activity, with EC_{50} values against *Pyricularia oryzae* Cavgra, *F. graminearum*, *F. oxysporum*, *A. solani*, and *R. solani* of 34.2, 73.8, 73.7, 42.9, and 24.6 μmol L^{-1}, respectively, which are superior to those of the phenazine-1-carboxylic acids (33.2, 81.5, 186.5, 176.4, and 37.3 μmol L^{-1}, respectively). SAR studies indicate that when a benzyl group is introduced on the piperazine ring, the introduction of a *p*-CH_3 group on the benzyl ring leads to good antifungal activity. The introduction of *o*-CH_3 and *m*-CH_3 groups causes the antifungal activity to gradually decrease. Replacing *p*-CH_3 with C_2H_5 and *p*-$CH(CH_3)_2$ also leads to successive reductions

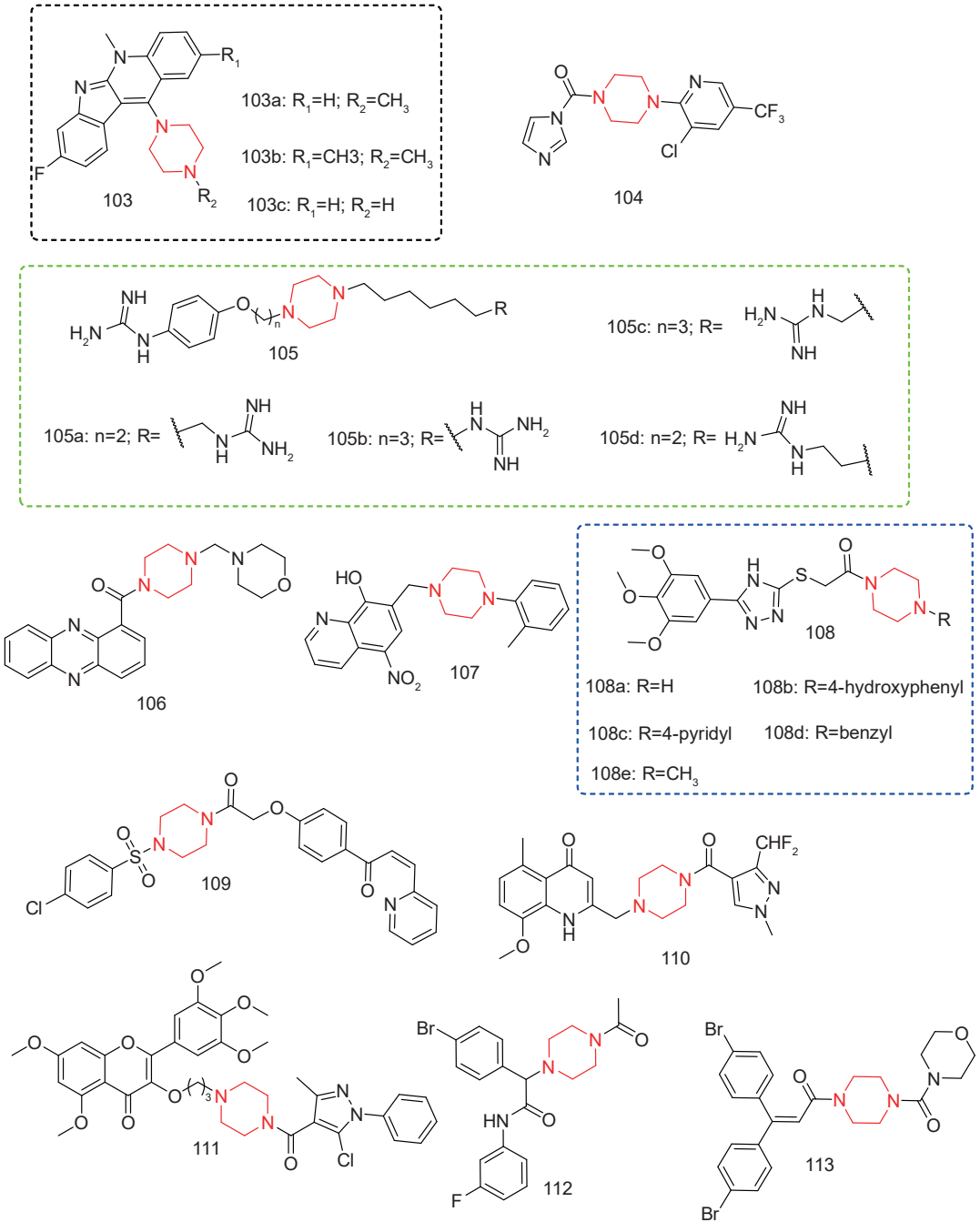


Fig. 15 Piperazine derivatives (103–113) with antifungal activity.

in antifungal activity. When Cl is introduced on the benzyl group, the position of the substitution has a significant impact on the antifungal activity of the compound. The introduction of *m*-Cl enhances the antifungal activity, whereas the *o*-Cl and *p*-Cl substitutions tend to reduce the antifungal activity. The antifungal activity of a derivative bearing an OCH_3 group in the *para* position of the benzyl group is higher than for derivatives with other substituents, and the antifungal activity of the *meta*-Cl substituted derivative is superior to those with CF_3, NO_2, and CH_3 groups. Thus, this research has provided lead compounds with higher activity for subsequent structure-optimization studies (Han *et al.* 2020).

The EC_{50} values of compound **107** (Fig. 15) for *Magnaporthe oryzae*, *F. oxysporum*. f. sp. *Vasinfectum*, *F. graminearum*, *S. sclerotiorum*, and *B. cinerea* are 0.0140, 0.0146, 0.0140, 0.0030, and 0.0124 mmol L^{-1}, respectively, which are better than those of azoxystrobin. SEM observations showed that **107** has a significant teratogenic effect on the mycelium morphology of *S. sclerotiorum*, which may explain its improved anti-*S. sclerotiorum* action (Yin *et al.* 2019). Amide piperazine derivatives have good antifungal activities against *B. cinerea*, *B. dothidea*, and *Phomopsis* sp. Among them, compounds **108a–d** (Fig. 15) exhibit good inhibition of *B. cinerea*, with inhibition rates of 91.8, 90.1, 93.6, and 91.2% at 50 mg L^{-1} that are superior to those of the control, Pyrimethanil (82.8%). The inhibition rate of compound **108e** (Fig. 15) against *Phomopsis* sp. is 92.4%, which is superior to that of the control, Pyrimethanil (85.1%). SAR studies indicate that when an alkyl group is substituted on the piperazine ring, smaller groups tend to lead to higher antifungal activities for *B. cinerea* and *B. dothidea*; and the highest antifungal activity against *Phomopsis* sp. was achieved with a CH_3 substituent. When a phenyl group was introduced on the piperazine ring, the inclusion of different electron-donating groups at the 4-position of the phenyl group modify the antifungal activities against *B. cinerea*, *Phomopsis* sp., and *B. dothidea*. While the introduction of OH leads to good activity, the introduction of NO_2 and CF_3 progressively reduce the antifungal activity of the compound (Wu *et al.* 2020). Structure-activity analysis showed that compound **109** (Fig. 15), which contains a pyridine ring, has the best inhibitory effects against *Alternaria brassicae* and *C. capsici*, with EC_{50} values of 9.9 mg L^{-1} that were superior to those of azoxystrobin (14.9 and 19.2 mg L^{-1}). The presence of electron-rich groups is not conducive to fungal inhibition. SEM analyses of the morphology of *R. solani* reveal that, upon exposure to **109**, the mycelium grow irregularly, shrink, and break (Zhou *et al.* 2022). Compound **110** (Fig. 15) shows antifungal activity against *R. solani* (38.3%) that is lower than that of the controls Fluopyram (61.5%) and Carbendazim (100%) (Fang *et al.* 2022). Piperazine rings introduced on myricetin give the derivative **111** (Fig. 15), which exhibits an *in vitro* EC_{50} for *Phomopsis* sp. of 16.9 mg L^{-1}, which is better than those of the control compounds fluopyram (71.8 mg L^{-1}) and azoxystrobin (50.7 mg L^{-1}). In addition, the protective and therapeutic activities of **111** against postharvest kiwifruit are 74.9 and 60.6%, respectively. Mycelium fracture, uneven thickness, and increased branching were observed after treatment, and exposure to **111** damaged the cell membrane by increasing the content of malondialdehyde, suggesting that it may act as an inhibitor of succinate dehydrogenase (Liu *et al.* 2023). Compound **112** (Fig. 15), obtained by introducing piperazine rings into mandelic acid, shows good antifungal activity *in vitro* and *in vivo* against *Monilinia fructicola*. The inhibition of mycelial growth by **112** may be related to disruption of the cell membrane, increased membrane permeability, and induced ROS production (Zheng *et al.* 2024). Compound **113** (Fig. 15) has positive effects on *Phomopsis* sp., *Aspergillus flavus*, *B. cinerea*, *S. sclerotiorum*, and *Colletotrichum fructicola*, with higher antifungal activities than azoxystrobin and dimethomorph (Chen *et al.* 2024).

2.5. Herbicidal activity

Piperazine derivatives have been less intensively studied in the field of herbicides. Biological activity studies showed that compound **114** (Fig. 16) exhibits no herbicidal activity by pre-emergence soil treatment. With the treatment of stems and leaves, the compound has no activity against barnyard grass, crabgrass, or *Amaranthus retroflexus*, but exhibits 27.1% inhibition of rape. Compound **114** shows no anti-TMV activity (Li *et al.* 2000). The inhibition rates of compounds **115a** and **115b** (Fig. 16) against rape root are 24 and 18.3%, respectively, and the inhibition rates against barnyard grass are 15.9 and 17.5%, respectively, at 100 mg L^{-1}. The inhibition rates of **115a** and **115b** on KARI are 8.0 and 33.9%, respectively, at 200 mg L^{-1} (He *et al.* 2006). The growth inhibition rates of the piperazine derivative Aspernigerin (**27a**) against *Cucumis sativus*, *Triticum aestivum* and *Echinochola crusgalli* are all above 90% at 500 mg L^{-1}, while the inhibition rates on *Sorghum bicolor*, *Raphanus sativus*, and *Brassica napus* are low. Further research on compound **27a**, which may become a natural lead compound for safe and green new pesticides, is thus warranted (Wu *et al.* 2012a). The concentrations required to inhibit 90% of the activity (IC_{90}) of compound **116** (Fig. 16) against *Amaranthus mangostanus* L., *Brassica chinensis*, *Sorghum sudanense*, and *Oryza sativa* are 11.7, 16.8, 20.7, and 18.1 mg L^{-1}, respectively. The results of 3D QSAR studies indicated that the introduction of amino groups has a significant impact on the herbicidal activity of the target compounds; however, if the introduced amino group contains oxygen atoms, the herbicidal activity is greatly reduced. When the piperazine ring is replaced with piperidine, the herbicidal activity does not change significantly, but if a carboxylic acid group is introduced on the piperidine, the herbicidal activity is greatly reduced. In addition, when piperazine is replaced with oxygen-containing morpholine, a significant reduction in herbicidal activity is observed (Ma *et al.* 2015).

2.6. Acaricidal activity

Mites can destroy the normal physiological functions of plants, affect their normal growth, and lead to reduced crop yields. With the large-scale use of pesticides, the resistance of mites to existing acaricides has increased, so new acaricides need to be developed. Piperazine itself has excellent biological activity, but there are few studies on this compound as an acaricide. The acaricidal

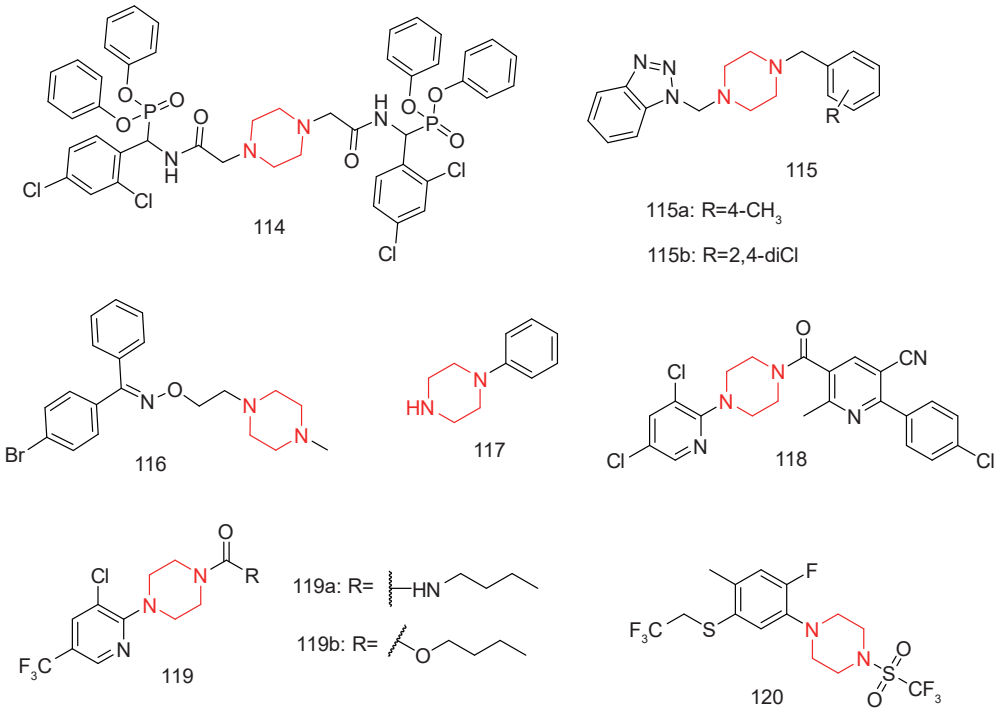


Fig. 16 Piperazine derivatives (114–116) with herbicidal activity and (117–120) with acaricidal activity.

activities of compound **117** (Fig. 16) against *Tyrophagus putrescentiae* (Schrank), *D. pteronyssinus* (Troussart), and *Dermatophagoides farinae* (Hughes) were tested using filter paper and fumigation methods. In the fumigation test, the LD_{50} values for **117** against *D. pteronyssinus* and *D. farinae* are 4.9 and 7.8 mg cm^{-2}, which are better than those for DEET (30.3 and 36.8 mg cm^{-2}, respectively). The filter paper tests gave LD_{50} values for **117** against *D. pteronyssinus* and *D. farinae* of 2.6 and 4.8 mg cm^{-2}, respectively, which are better than those for DEET (12.5 and 20.6 mg cm^{-2}, respectively). However, except for piperazine, piperazine derivatives have no activity against *T. putrescentiae*. Compound **117** can be used as a good mite indicator based on the color change it induces. The results demonstrate that piperazine derivatives have excellent activity and can act as indicators, so they have the potential to replace existing problematic acaricides (Lee *et al.* 2009). Compound **118** (Fig. 16) exhibits good inhibitory activity against adults of *T. cinnabarinus*, with an LC_{50} of 0.8977 mg L^{-1} in greenhouse tests, which is higher than those of the control compounds Spirodiclofen and Pyridaben. The biological activity results with the larvae and eggs of *T. cinnabarinus* indicate that the larvicidal activity of compound **118** is higher than that of Pyridaben but comparable to that of Spirodiclofen. The egg-killing activity of compound **118** is higher than that of Spirodiclofen but lower than that of Pyridaben. In addition, field test results showed that compound **118** can work rapidly and persistently, thereby effectively controlling *Panonychus citri* and *P. ulmi*. Therefore, compound **118** may constitute a new acaricide for controlling *T. cinnabarinus* and potentially *P. ulmi* and *P. citri* (Xie *et al.* 2017). The fluorine-containing pyridazine piperazine urea derivative **119a** (Fig. 16) has a lethal effect on harmful mites and mite eggs, so it can be used as an acaricide for agricultural mite control. The acaricidal activity of **119a** on mite eggs is 100% at 10 mg L^{-1}, which is equivalent to that of the control compound, Spirodiclofen (100%). The activity of compound **119a** on mite eggs is 94% at 1 mg L^{-1}, which is better than that of the control, Spirodiclofen (71%) (Wang *et al.* 2018b). The fluoropyridine piperazine amide derivatives have good inhibitory effects on harmful mites and mite eggs, so they can be used as acaricides for the prevention and control of mite damage in agriculture and forestry. All the target compounds show high activity on mite eggs and most of the compounds have an acaricidal activity of more than 90% at 1 mg L^{-1}, which is higher than that of the control, Spirodiclofen. Compound **119b** (Fig. 16) is especially active: at 1 mg L^{-1}, its acaricidal activity against eggs is 96%, which is significantly better than that of Spirodiclofen (72%) (Wang *et al.* 2018a). Compound **120** (Fig. 16) shows good activity against *P. citri*, *Tetranychus kanzawai*, and *Tetranychus urticae*. There is no interspecific selection, and SAR studies showed that the substitution of a trifluoroethyl group on the S atom gave the highest acaricidal activity, while the presence of an F atom on the benzene ring and the substitution of a piperazine trifluoromethyl sulfonyl chloride improve the acaricidal activity; and changes to one of the three substituents lead to reduced activity (Suzuki *et al.* 2021).

3. Mechanism of action

Studies on the mechanism of insecticidal activity of piperazine derivatives are limited. The existing studies have involved docking the compounds with acetylcholinesterase (AChE) to verify their binding, but the mechanism of action has not

been examined in depth (Wang *et al.* 2014; Knutsson *et al.* 2018). Few studies on the mechanism of herbicidal activity of piperazine derivatives have been conducted. The affinity between the compounds and ketol acid reductoisomerase (KARI) has been tested, but no further studies have been conducted (He *et al.* 2006; Wang *et al.* 2015a, 2016d, 2017; Zhang B L *et al.* 2016a).

3.1. Mechanism of anti-plant virus agents

Studies on the mechanism of action of piperazine derivatives on plant viruses are mostly based on CP or N protein as the target protein. After identifying the possible binding site of small molecules to the CP or N protein through molecular docking, amino acids at the putative active site were mutated and their importance was verified *in vitro* and *in vivo*. Studies have shown that most compounds bind to the CP or N protein through hydrogen bonding, which affects protein function, inhibits virus assembly, and further reduces virus replication, thus achieving the antiviral effects. In addition, the mechanism of action of many compounds is based on the antiviral protective activity of small molecules. Proteomics, defensive enzyme activity tests, and chlorophyll content determination have been used to identify the possible antiviral actions of small molecules. Most of these studies have shown that small molecules may act on certain signalling pathways, activate defensive enzyme activity, and induce host resistance, thereby inhibiting viral infection.

Compound **57** binds to TMV helicase and TMV CP to inhibit viral replication (Nagalakshmamma *et al.* 2020). Compound **58a** binds strongly to TSWV N protein, which may hinder the formation of N protein polymers by preventing binding to the N protein, thereby disrupting ribonucleoprotein complex formation, and preventing virus replication (Jiang *et al.* 2021a). Compound **58b** has a strong affinity for ToCVCP and can inhibit the expression of the *ToCVCP* gene in *Nicotiana benthamiana*, thereby inhibiting virus proliferation (Jiang *et al.* 2021b). The results of proteomics, defensive enzyme activity, and chlorophyll content tests indicate that compound **58c** can enhance tobacco resistance to TMV by regulating the chlorophyll content and promoting photosynthesis (Yuan *et al.* 2022). Compound **58d** increases the activity of tobacco defensive enzymes, activates the glycolytic/gluconeogenic pathway, and improves tobacco resistance to PVY (Li *et al.* 2022). Compound **58e** induces the oxidative phosphorylation pathway by activating the expression of defensive enzymes and improving the resistance of tobacco to TSWV (Zhang W B *et al.* 2024). Molecular docking showed that compound **58f** is hydrogen bonded to amino acids Lys68, Thr92, and Arg94 of TSWV N protein, among which Thr92 and Arg94 are located in the disordered region of the N protein. Both *in vivo* and *in vitro* experiments showed that these three amino acids are key sites for **58f** binding to the N protein. Further studies showed that simultaneous mutation of the three amino acid sites affects the formation of N-protein condensates resulting from phase separation and inhibits the proliferation of TSWV in *N. benthamiana*. In addition, N protein promotes the formation of N-protein condensates by interacting with the host protein NbRANL (Wang *et al.* 2025). After TMV-GFP infected *N. benthamiana* was treated with compound **59**, both RT-qPCR and Western blot analysis showed reduced expression of the *GFP* gene and GFP protein in *N. benthamiana*, which inhibited TMV infection but had little effect on TMV particle morphology (Ji *et al.* 2022). Representative compound mechanisms for pathway mapping are shown in Fig. 17.

3.2. Mechanism of antibacterial action

Most studies on the bacteriostatic mechanism of piperazine derivatives have involved using SEM to observe the effect of small molecule treatment on the surface morphology of bacteria and then identifying possible mechanisms of action through proteomics and defensive enzyme activity tests. The results show that the bacteriostatic mechanism of most small molecules is related to the destruction of the bacterial cell membrane, changes to bacterial cell membrane permeability, and the generation of ROS. The antibacterial effect may also be achieved through the modification of signalling pathways.

Compound **71** can induce cell apoptosis, damage cell membranes, reduce defensive enzyme activity, and induce ROS generation (Wang *et al.* 2020). Compounds **72** and **71** have almost the same mode of action (Xiang *et al.* 2020). Compound **75** can damage the surface of *Xoc*, reduce the content of exopolysaccharides (EPS), increase cell membrane permeability, reduce bacterial movement, and inhibit extracellular amylase activity. The Type III secretion system also affects the assembly of *Xoc* flagella (An *et al.* 2024). Compound **76** can inhibit bacterial infection by causing damage to the cell membranes, leading to protein overflow, and inhibiting the synthesis of proteins by binding to DNA (Ma *et al.* 2024). Compound **77** can damage the bacterial cell membrane, induce ROS production, regulate the chlorophyll content, activate the ABA signalling pathway in rice, and activate rice defensive enzymes such as superoxide dismutase (SOD), phenylalanine aminolyase (PAL), peroxidase (POD), and catalase (CAT) (Wang *et al.* 2024). Compound **78** can damage the bacterial cell membrane, reduce the expression of EPS, inhibit the growth of biofilms, regulate the chlorophyll content, enhance the activities of defensive enzymes (POD, SOD, CAT), promote photosynthesis, and enhance the disease resistance and defensive ability of plants (Zeng *et al.* 2024). A pathway diagram showing the mechanism of action of representative compounds is presented in Fig. 18.

4. Conclusions and outlook

Piperazines are a class of compounds with extensive agricultural biological activities. Through our comprehensive review of pesticidal activities and molecular mechanisms, piperazine derivatives can be classified based on 11 structural characteristics. (1) Piperazine that is mixed with other compounds, such as piperazine citrate and piperazine ferulate tablets. (2) Only one NH of the piperazine is replaced, and the second is exposed. (3) Both NHs of piperazine are replaced with carbonyl and sulfonyl groups. (4) The NHs of piperazine are replaced with carbonyl and alkyl chains. (5) The NHs of piperazine are replaced with

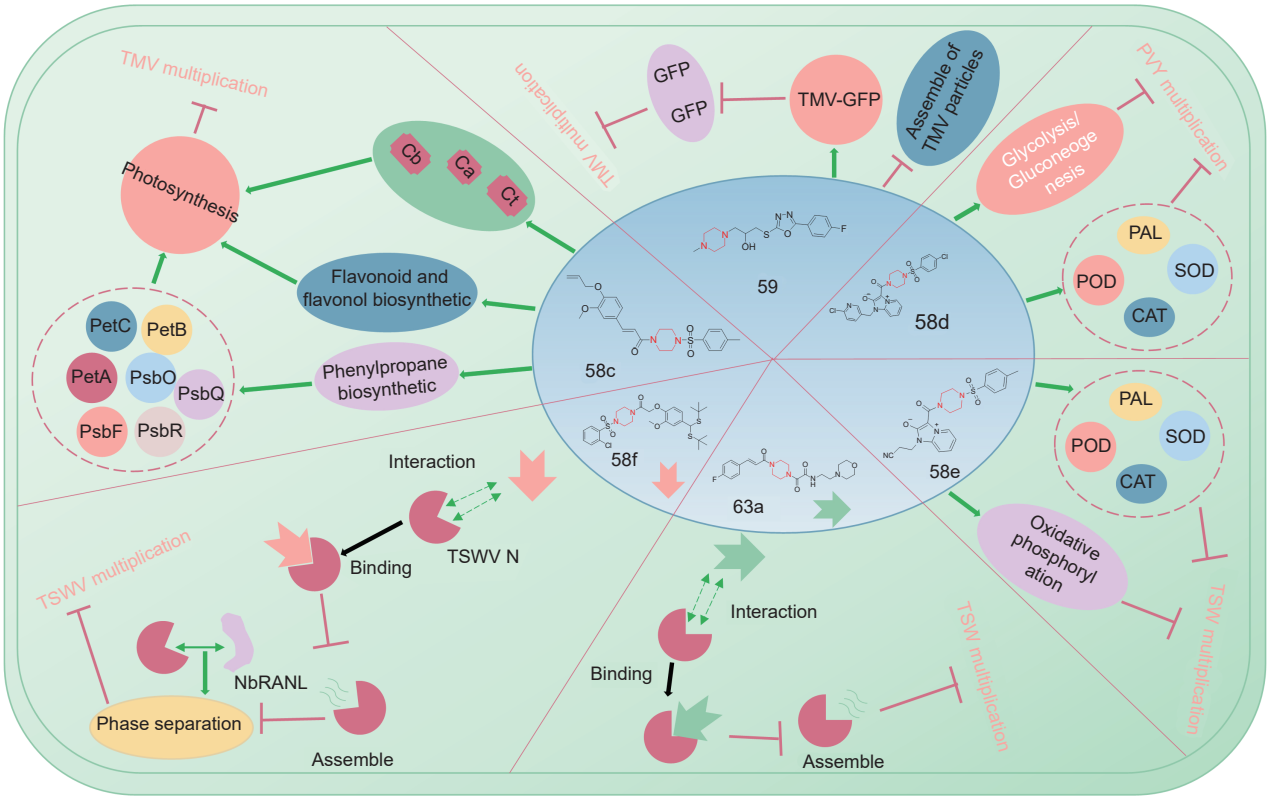


Fig. 17 The mechanism pathway diagram of piperazine derivatives with anti-plant virus activity.

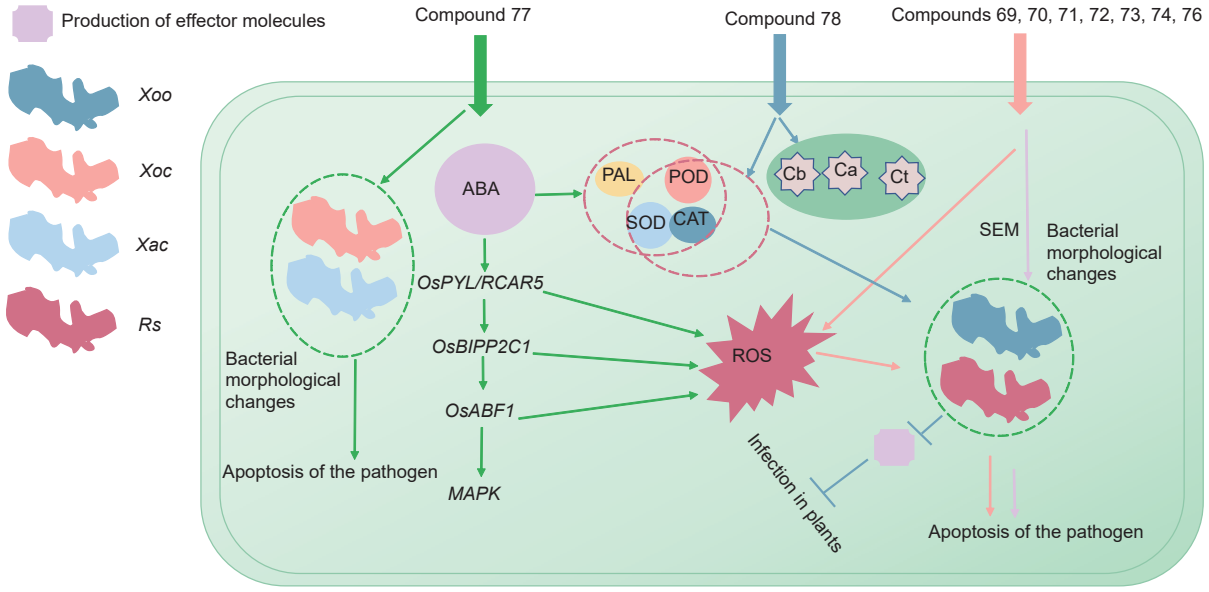


Fig. 18 The mechanism pathway diagram of piperazine derivatives with antibacterial activity.

sulfonyl and alkyl chains. (6) Both NHs of piperazine are replaced with carbonyl groups. (7) Both piperazine NHs are replaced with alkyl chains. (8) Piperazine is replaced with carbonyl and aryl groups at both NHs. (9) Piperazine NHs are replaced with alkyl and aryl groups. (10) Piperazine is replaced with aryl groups at both NHs. (11) Piperazine is replaced at both NHs with sulfonyl and aryl groups.

The insecticidal activity of piperazine derivatives is the most intensively studied of their pesticidal activities. Perhaps most researchers are basing their research on the insecticidal and repellent activity of piperazine itself, such as the existing commercial drug piperazine citrate. Its antifungal activity has also been studied in more depth because it is based on an existing systemic fungicide, Triforine, which is a piperazine-like heterocyclic compound. Moreover, in terms of the anti-plant-virus activity of piperazine derivatives, most studies

have linked the NHs of piperazine rings to amide and sulfonamide structures, respectively. Such compounds have good anti-ToCV, PVY, TMV, CMV, and TSWV activities, and the mechanism of action of these compounds has been studied extensively. Most of the results show that these compounds can act on the coat protein of the virus to reduce its pathogenicity by affecting the assembly of the virus, or by binding to the disordered regions on the N protein to affect the formation of N-protein condensates induced by phase separation and ultimately reduce the pathogenicity of the virus.

In summary, piperazine is an important class of nitrogen-containing heterocyclic compounds. Due to its low acute toxicity to mammals, piperazine has been identified as an important direction for the development of heterocyclic green pesticides. This review provides a comprehensive summary of the applications of piperazine derivatives in pesticide development. In future studies, piperazine pesticides can be developed further by introducing different substituents according to the different control objects. For example, bialkyl chains or aryl and alkyl chains are primarily used to enhance the insecticidal and antifungal activities, while the introduction of carbonyl and sulfonyl groups at the same time can enhance the antiviral activity. However, it is also possible that the introduction of disulfonyl groups could result in more effective antiviral agents. In addition, the structure may also be optimized by modifying bioelectronic isosteric analogues and active fragmentation virtual screening of piperazine derivatives. Currently, relatively little is known of the mechanisms through which piperazine derivatives exhibit their agricultural activities and only antiviral drugs have been studied in depth. Most antiviral drugs have been shown to act on viral coat proteins, and these compounds hinder viral infection by binding to the coat proteins and affecting viral proliferation or nucleocapsid protein phase separation. This information can be useful for guiding further developments in this field. However, some areas still need to be strengthened, such as the selection of target proteins. Thus, alkynyl or acridinium groups linked to small molecules can be used together with photocrosslinking techniques to capture and identify the potential viral protein targets. In this way, the range of possible piperazine derivative targets can be extended and broadened further.

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Declarations of competing interest

The authors declare that they have no conflicts of interest.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that they did not use AI in the preparation and writing of this manuscript.

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