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# Hydrazone derivatives in agrochemical discovery and development

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## ABSTRACT

As a common active substructure, hydrazone has attracted increasing attention and is considered essential for pesticide discovery. It has been widely regarded as a potential insecticidal, antibacterial, anti-fungal, antiviral, and herbicidal agent. In this review, we highlight the pesticide versatility of hydrazone fragments and provide a comprehensive summary of the biological activity, structure-activity relationship analysis (SARs), and primary mechanism of their analogs. This profile is expected to give valuable information for discovering new pesticides.

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## 1. Introduction

With a chemical versatility trait of  $-NH=N=CH-$ , hydrazone is the most typical example of a Schiff base, which is a vast group of compounds containing a double bond between carbon and nitrogen atoms [1]. Hydrazone with a  $C=N$  bond is conjugated with a pair of nitrogen atoms nucleophilic electrons. The carbon atom has both nucleophilic and electrophilic properties, and the  $\alpha$ -hydrogen herein is more potent than that of acidic ketones [2]. The truths mentioned above make hydrazone a special structure among the organic compounds, especially to be distinguished from imines and oximes. Due to the special structural-functional characteristic of triatomic  $C=N-N$ , hydrazone is widely used as the reagent for multiple synthesis chemistry, such as hydrazone iodination for the synthesis of alkenyl iodide [3], pyrazole rings by hydrazone [4] and the reduction of hydrazones for the synthesis of chiral amines [5]. Hydrazone is a fundamental element for the production of heterocyclic compounds, for instance, coumarins [6] and 1,3-thiazolidine-4-ones [7], which are essential for many biological processes. Hydrazone Schiff bases are present in many biological molecules showing various bioactivities. In 2007, the biological activities of hydrazone derivatives were first reviewed, in which Rollas *et al.* identified seventy-one hydrazone derivatives

showing pharmacological activities, including anticonvulsant, antidepressant, analgesic, anti-inflammatory, antiplatelet, antimalarial, antimicrobial, antimycobacterial, antitumoral, *etc.* [8]. In addition, hydrazone has a wide range of applications in anti-cancer [9,10]. The  $-NH$  in the hydrazone structure can be bound to Arg 929 to form hydrogen bonds and exert anticancer effects [10]. Since natural products are a critical inspiration for the design of bioactive molecules, Omidi *et al.* reviewed hydrazone derivatives showing various biological activities based on the natural product curcumin [11]. There are also reviews reporting significant biological activities of the complexation of hydrazone with metals, in which hydrazone was used as an important ligand [12]. The use of the structure for  $-NH=N=CH-$  of hydrazone has been reported in response to the pH environment, and hydrazone-based materials responsible for releasing payloads at specific pH conditions of tumor or infection sites have also been reviewed [13].

In particular, hydrazide-hydrazones, and benzene sulfonyl hydrazones are the most studied hydrazone derivatives, and their biological activities have also been reviewed to guide the development of hydrazone-based drug design [14–16]. Moreover, compared to hydrazine, hydrazone has been observed to be much less toxic to the liver, kidneys, and lungs, which has led to increased attention [17]. The synthesis of hydrazone derivatives provides an opportunity for chemists to explore more efficient methods for obtaining molecules for synthesizing biological molecules. Hydrazide-hydrazones and benzene sulfonyl hydrazones are two of the most studied hydrazone derivatives, and their biological activities have been reviewed to inform the development of hydrazone-

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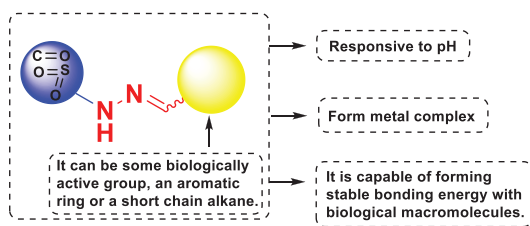


Fig. 1. Structural characteristics of hydrazones.

based drug design. The special structure of hydrazone  $\text{-NH-N=CH-}$  with the additional donor site ( $\text{C=O}$ ,  $\text{O=S=O}$ ) has captivated researchers due to its interesting biological characteristics (Fig. 1). Studies show that the oxygen atom on the donor site  $\text{C=O}$  and the nitrogen atom on  $\text{C=N}$  could form stable hydrogen bonds with the hydrogen atoms in biological macromolecules, while as electron donors, sulfur and other atoms in biological macromolecules could also form hydrogen bonds with the hydrogen atoms on nitrogen, which further enhance its biological activity (Fig. 1) [18]. Wahbeh *et al.* conducted a study to improve the properties of hydrazone and its utilization in the medical field while considering its pH sensitivity and compatibility with other functional groups [19]. From the reviews above, we found that hydrazones possess a wide range of biological activities due to their ability to form complexes with transition metals, be responsive to pH, and bind to other structures ( $\text{C=O}$ ,  $\text{O=S=O}$ ). For these extensive biological activities, researchers have systematically summarized them. However, these reviews are only medicinal related, and their mechanisms have never been reviewed. To our knowledge, hydrazone has also been active in agricultural chemistry for decades [20,21]. For example, as early as 1955, the first commercial fungicide benquinox (Fig. S1 in Supporting information) containing hydrazone was reported [22]. Subsequently, pesticide workers successively reported commercial pesticides containing hydrazones, such as the fungicide ferimzone [23] and the herbicide diflufenzopyr [24], and the insecticide hydramethylnon [25] metaflumizon (Fig. S1) [26]. Hydrazone has indeed drawn much attention to chemistry for its various biological activities. Still, regarding pesticides, people only briefly describe the biological activities of halogenated hydrazone derivatives [27]. Hydrazone has been utilized in the field of pest control for many years; however, there is still a need for a comprehensive review to guide the design and synthesis of hydrazone for further development. This article seeks to analyze the recent research advancements regarding hydrazone derivatives in terms of their insecticidal, antibacterial, antiviral, and herbicidal properties. We will focus on the design of hydrazones, as well as the structure-activity relationship and mechanism of action of these compounds. This subject will provide a valuable source of information for pesticide researchers interested in pesticide design based on hydrazone.

## 2. Insecticidal activity

### 2.1. Hydrazone insecticide containing a benzene ring

Humans will still face the problem of food shortages, especially in remote areas or developing countries [28]. It is understood that crop pests have always been one of the main factors that cause crop yields to be greatly reduced [29]. Hence, it is necessary to develop insecticides with high insecticidal activity. In 1973, DuPont discovered benzophenone hydrazone compounds (Fig. 2, 1) that possessed remarkable insecticidal properties. These compounds had simple preparation, excellent activity, a wide action spectrum, and low toxicity [30]. Since then, such type of com-

pounds has attracted the interest of many pesticide companies and scientific researchers. Several international companies, including Basf, Sumitomo, DuPont, and Bayer, have identified various benzophenone hydrazone derivatives with pesticide properties. Subsequently, the benzophenone hydrazone derivative tosylsulfur hydrazone (Fig. 2, 2) developed by the Zhejiang Research Institute of the Chemical Industry had shown high insecticidal activity against lepidopteran pests. It was expected to become a new type of insecticide [31]. The insertion of the carbonyl group makes this kind of compound 3 (Fig. 2) have a better insecticidal effect [32]. Scholars introduced a six-membered ring based on derivative 3 for modification to obtain compound 4 (Fig. 2) but found that its insecticidal activity was not effectively improved after such structural modification [33]. If the  $\text{-SCH}_3$ ,  $\text{-SO}_2\text{CH}_3$ ,  $\text{-OSO}_2\text{CH}_3$  on the benzene ring of derivative 3 was changed to  $\text{-OCF}_3$ ,  $\text{-OCF}_2\text{Br}$ ,  $\text{-OCF}_2\text{CF}_2\text{Br}$  to give compound 5 (Fig. 2), it was effective against *Spodoptera littoralis* (*S. littoralis*) with insecticidal activity  $>80\%$  at 400 mg/L [34]. By introducing a methylene group to the left side of S, a benzophenone derivative 6 (Fig. 2) with better insecticidal activity could be obtained. The lethality rate of *S. litura* larvae and other pests reached to 100% [35]. In addition, the introduction of a sulfonyl group on N in derivative 6 could greatly improve the insecticidal activity of derivative 7 (Fig. 2), and its lethality against *P. xylostella* and *Spodoptera litura* (*S. litura*) at a lower concentration (10 mg/L) reached to 70%. Surprisingly, such derivatives also possess excellent properties, including low toxicity, persistence, and high selectivity [36]. In 2001, Manfred Boger carried out many modifications and derivations of benzophenone (Fig. 2, 8), and they found that when X was a halogen atom substituted at the 4-position of the benzene ring, the insecticidal activity could be enhanced; R' and R'' can also improve the insecticidal activity of the compound when it was a short-chain alkane or hydrogen atom; when R''' was a sulfur atom or an oxygen atom, it has almost no effect on the insecticidal activity; when Y was  $\text{-OSO}_2\text{CF}_3$ ,  $\text{-OCF}_2\text{Br}$ , and  $\text{-OCF}_2\text{Cl}$ , it could show excellent performance and almost no insecticidal activity when Y was a group of  $\text{-SOCF}_3$  [37]. The installation of acyl ureas and acyl thioureas into benzophenone fragments resulted in the formation of benzophenone derivative 9 (Fig. 2). This compound exhibited remarkable insecticidal activity and had a broader insecticidal range. These derivatives not only had a good control effect on *Brevicoryne brassicae* (*B. brassicae*) but also had an excellent acaricidal effect on *Tetranychus cinnabarinus* (*T. cinnabarinus*). Compound 9 had the best acaricidal activity against *Tetranychus cinnabarinus*, with an  $\text{LC}_{50}$  value of 0.305 mmol/L [38]. The thienyl group was used to replace the phenyl group to obtain derivative 10 (Fig. 2) with better insecticidal activity, which showed good activities against Hemipteran pests and parasitic nematodes in green bean plants, *etc.* [39]. In addition, the benzophenone derivatives invented by Kobe and Xia also had good insecticidal activities [40–42]. The modification and derivation of benzophenone were found to be enhanced by the inclusion of a carbonyl group and sulfonyl group, which in turn improved its insecticidal activity. This is due to the improved interaction between small molecules and biological macromolecules.

Metaflumizon is a new type of semicarbazone insecticide derived from the compound 3-phenyl-1-phenylcarbamoyl-2-pyrazoline [43,44]. In 2006, it was first registered in Colombia and sold under the trade name Verismo SC. Subsequently, it was approved to be registered in EU countries such as Greece, Austria, and Germany under the trade name Alverde. It is mainly used for controlling *Leptinotarsa decemlineatas* (*L. decemlineatas*) [45]. Metaflumizon has a new mechanism of action and is a neuronal sodium channel blocker. Attaching to the receptors of sodium ion channels blocks the passage of sodium ions through the axonal membrane, thereby inhibiting nerve impulses, leading to excessive relaxation, paralysis, and eventual death of the pest [46].

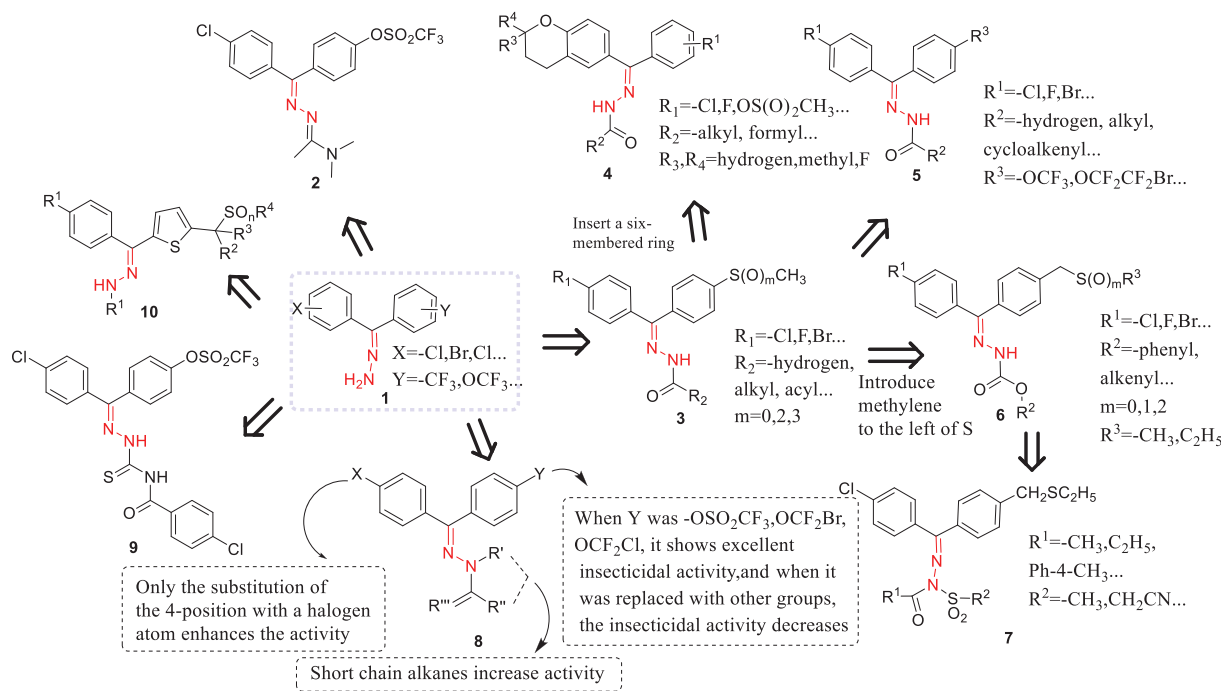


Fig. 2. Benzophenone hydrazone derivatives.

Metaflumizone effectively controls lepidopteran larvae, coleopteran larvae, and adults, primarily through ingestion and stomach poisoning [46]. Since then, researchers have modified the Metaflumizone derivative and found that compound **11** (Fig. S2 in Supporting information) has a better control effect against *S. exigua* Hübner, *H. armigera* Hübner, *P. xylostella* and *Pieris rapae* (*P. rapae*) than Metaflumizone [47]. Halometzone is a metabolic inhibitor that can eliminate pests by inhibiting complex III on the inner membrane of mitochondria to stop oxidative phosphorylation. It is mainly used to control *Blattodea* and *Myrmecolacidae* [48]. Its derivatives **12** and **13** (Fig. S2) also had excellent insecticidal activity [49,50]. The principle of active substructure splicing is the most effective method for discovering highly efficient biologically active molecules [51]. By employing this technique, many compounds with high activity and no adverse effects on humans and nontarget organisms have been discovered. For instance, substituted phenyl, cycloalkane, and heterocycle active substructures have been combined with hydrazone fragments to generate numerous hydrazone derivatives with remarkable insecticidal activity [52]. As early as 1995, European chemists combined trifluoromethyl phenyl and hydrazone fragments to produce compound skeletons with outstanding insecticidal activity, of which derivative **14** (Fig. S3 in Supporting information) had remarkable insecticidal activities against *Diabrotica virgifera virgifera* (*D. virgifera virgifera*) with lethality rates >90% at 10 mg/L. Interestingly, when the author introduced a sulfonyl group into such a structure, not only could the original high activity be retained, but the insecticidal activity spectrum of this compound could also be effectively broadened. For example, compound **15** (Fig. S3) not only had significant insecticidal activities against *Spodoptera eridania* and *D. virgifera virgifera* but also had a good control effect on two-spotted spider mites and potato leafhoppers [53]. Compound **16** (Fig. S3) had very good and broad-spectrum insecticidal activities against plant-parasitic and animal-parasitic pests [54]. Diaminoguanidine hydrazone derivatives **17** (Fig. S3) were also a class of active compounds with excellent insecticidal activity [55]. Compounds **18**, **19** and **20** (Fig. S3) had good insecticidal activities against *S. armyworm*. The compounds had more than 75% insecticidal activity on above mentioned pests at 300 mg/L.

Results indicated that sulfonylhydrazone derivatives had a superior insecticidal effect in comparison to other hydrazone derivatives [56]. Yagi Kazuo conducted extensive research on amido ketone derivative **21** (Fig. S3) and found that novel 5- or 6-membered heterocyclic substituted amido ketone derivatives and their salts exhibited excellent insecticide properties even at low doses. Additionally, such derivatives have no adverse effects on mammals, fish, and beneficial insects [57]. Compound **22** (Fig. S3) containing substituted benzene also had certain insecticidal activity [58]. The alkanesulfonyl hydrazone derivative **23** (Fig. S3) had a wide range of biological activities, including those of pests, fungi, and weeds [59]. In addition, hydrazone derivatives **24** and **25** (Fig. S3) with cycloalkyl structures also had certain insecticidal activity [60,61].

Through a literature survey, we found a large number of Japanese patents describing that derivatives containing hydrazone fragments have insecticidal activity. The compounds mentioned in these patents have not only diverse structures, excellent insecticidal activity, and a broad spectrum of insecticidal activity but also excellent characteristics, such as being friendly to the environment and friendly to humans and beneficial organisms. For example, the hydrazone derivative **26** (Fig. S4 in Supporting information) invented by Kawada Shinji exhibited a broad spectrum and excellent insecticidal activity. It could be used to prevent and control arthropods and other pests. In particular, it had an excellent control effect on harmful insects in agricultural art [62]. Derivative **27** (Fig. S4) also had broad-spectrum insecticidal activity and effective against those pests with strong resistance. At a concentration of 500 mg/L, some compounds had 100% mortality to *Spodoptera litura* (*S. litura*), *Adoxophyes sp* (*A. sp*) and *P. xylostella* [63]. In addition, derivatives **28**, **29a-29e** and **30** (Fig. S4) also had certain insecticidal activities [64–66]. However, inserting simple aromatic groups into the hydrazone fragment resulted in satisfactory insecticidal activity. For example, inserting substituted phenyl groups or five-membered heterocyclic groups at the left and right ends of the acyl hydrazone fragment could give **31** (Fig. S4). This compound showed an extraordinary lethality rate against *A. aegypti*; the lethality rate of compound **31** to *Aedes aegypti* larvae was 100% [67]. Furthermore, the hydrazone derivative **32** (Fig. S4) created by

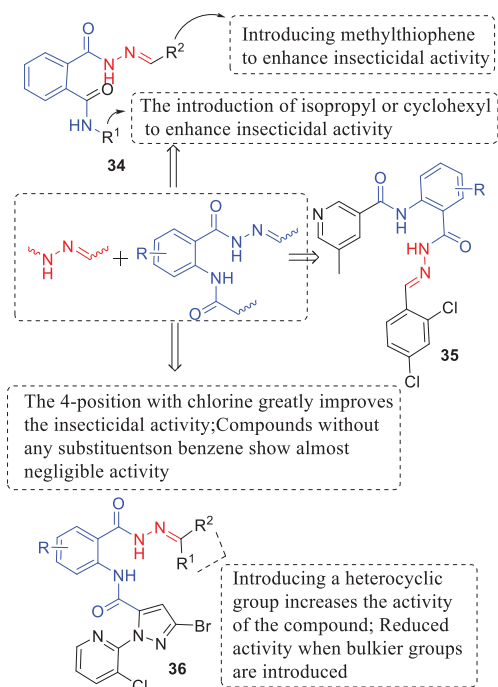


Fig. 3. Hydrazone derivatives containing phthalimide and benzene ring.

replacing the acyl hydrazone segment in compound **31** with hydrazone displayed remarkable nematocidal activity with an  $LC_{50}$  of 23.3 mg/L. Metabolomic analysis conducted via GC-MS revealed that compound **32** was highly effective in elevating fatty acid levels [68]. The hydrazone derivative synthesized with paeonol as the base exhibited nematocidal activity, with compound **33** (Fig. S4) displaying an  $LC_{50}$  of 45.1 mg/L [69].

Flubendiamide is a commercial pesticide developed by a Japanese pesticide company. It has good activity against all lepidopteran pests and has excellent characteristics, such as fast action speed and long-lasting effects [70]. Inspired by this, Liu took it as a guide and introduced a hydrazone fragment to obtain phthalimide derivatives (Fig. 3), which had good control effects against *M. persicae*. In particular, the insecticidal activity of compound **34** ( $LC_{50} = 58.9$  mg/L) was much higher than that of the control flubendiamide ( $LC_{50} = 184.0$  mg/L) [71]. When aromatic groups replaced the aliphatic compounds on the  $R^1$  group in derivative **34**, compound **35** (Fig. 3) was obtained with a wider insecticidal spectrum. In addition to the control effect against *M. persicae* and *P. xylostella*, compound **35** also had a control effect against *H. armigera*, *M. separata* and *C. pipiens pallens* [72]. Modification of the commercial insecticide chlorantraniliprole can yield hydrazone phthalimide derivatives with exceptional insecticidal potency and a broad insecticidal scope. Among them, the representative compound **36** (Fig. 3) may be due to the existence of a 4-position substituent electron-withdrawing group (chlorine) on the phenyl ring, which has effects against *P. xylostella* [73]. The comparative molecular field analysis (CoMFA) model proved that a 4-position substituent on the phenyl ring was beneficial [73].

## 2.2. Hydrazone pesticides containing heterocyclic rings

Heterocyclic compounds are a class of important structures that widely exist in nature and have become the mainstream of new pesticide development. They can be used as insecticides, herbicides, fungicides, and antiviral agents. For example, heterocyclic compounds containing triazine, oxadiazole, pyridine, and pyrimidine have excellent biological activity. Scientists installed hydra-

zone structure to pyrimidine to create a range of derivatives (Fig. S5 in Supporting information) with a wide-spectrum insecticidal capability, mainly effective against lepidopteran and coleopteran pests [74]. Acetylhydrazone derivatives (Fig. S5) containing pyrimidine structures had certain insecticidal activity against *Aedes aegypti* (*A. aegypti*). At a concentration of 0.01 mg/L, the mortality rate of the most active compound **38** (26.7%) was lower than that of permethrin (100%) [75]. Triazinyl phenylhydrazone derivative **39** (Fig. S5) also had certain insecticidal activity, and its control effect was outstanding in pest control, especially in lepidoptera or coleopteran pests [76]. Hydrazone derivatives **40** (Fig. S5) containing a 1,3,4-oxadiazole sulfide group had certain insecticidal activities against *P. xylostella*, *Vegetable aphid* (*V. aphid*), and *Empoasca viti* (*E. viti*) [77]. Pyridine-containing hydrazone derivatives **41** (Fig. S5) had broad-spectrum and significant insecticidal activity, and it was suitable for various agricultural, forestry, horticultural, and grain storage pests [78].

## 2.3. Halohydrazone insecticide

Hydrazone halide is also a good class of active substructures. As early as 1976, researchers invented insecticidal compounds with morphogenetic hormone-mimicking activity **42** (Fig. S6 in Supporting information) [79]. Derivative **43** (Fig. S6) containing hydrazone halide structures was observed to have broad-spectrum insecticidal qualities, proving to be a successful remedy for numerous pests [80].

## 2.4. Thiophosphate insecticide

In addition, thiophosphate hydrazone derivatives also have excellent insecticidal activities, such as derivatives **44** and **45** (Fig. S6), which could effectively control houseflies and other pests [81,82].

## 2.5. Hydrazone-like metal complex insecticide

As previously mentioned, hydrazone complexes have attracted much attention because of their structural characteristics (more description see Section S1 in Supporting information). The hydrazone-liganded complex **46** (Fig. S6) had good and broad biological activities against pests (*H. armigera* and *S. liturapests*), phytopathogenic fungi [*Fusarium oxysporum* (*F. oxysporum*), and *Macrophomina phaseolina* (*M. phaseolina*)], bacteria, etc. Although the activity is not as good as that of commercials, it still has a large space for development in the future, and it also provides a reference for the research of hydrazone complexes in the agricultural field [83]. Complex **47** (Fig. S6) also had a broad range of biological activities. Only chloroquinoline compounds had good fungicidal activity, while derivatives modified with pyrazole and pyrazine had moderate insecticidal activity. A unique trihydroxy hydrazone was active against both organisms. The metal complex-containing hydrazone was the most effective fungicide in this series, showing insecticidal activity only when complexed with  $Zn^{2+}$  ions [84].

## 2.6. Hydrazone pesticides containing natural products

For a long time, many natural product insecticides have been the first choice of green insecticides because of their safety for humans and non-target organisms and their environmental friendliness [85]. Xu's team has been committed to researching natural products hydrazone pesticides for many years [86–91]. Implemented the active substructure hydrazone into indole, cholesterol, piperine, and other natural products, discovering a number of compounds with unique structures and remarkable insecticidal

activity, and SARs of these compounds were systematically studied [86–91]. This study paves the way for the future design, structural modification, and development of hydrazone derivatives as pesticides. For example, they actively spliced the natural product indole with hydrazone structures to construct a series of derivatives **48** (Fig. S7 in Supporting information) with a good nematoda control effect ( $LC_{50} = 1.0$  mg/L) [86]. It was found that target compounds with excellent nematoda activity could be obtained by using  $R^1$  and  $R^2$  as electron-withdrawing substituents,  $R^3$  as methyl, and  $R^4$  as phenyl with electron-withdrawing substituents. The same year, they replaced indole with cholesterol and synthesized a series of hydrazone derivatives [87]. Among them, compound **49** (Fig. S7) showed the best insecticidal activity against *M. separata*, which may be related to the electron-withdrawing group ( $-NO_2$ ); The insecticidal activity of compound **49** (55.2%) against *M. separata* was higher than that of the positive control toosendanin (48.3%) at 1 mg/L [87]. Subsequently, the authors used piperine, podophyllotoxin, and osthole as lead compounds, introducing hydrazones to obtain compounds **50**, **51** and **52**, respectively (Fig. S7) [88–90]. Some target compounds were found to have good control effects against *M. separata* in the pupation, larval and adult stages and can be further developed as potential insecticides. The introduction of a phenyl ring at the C-2 position into the piperine hydrazone derivatives was important for their insecticidal activity [88], while the introduction of alkyl carbonyl or heterocycarbonyl reduced their insecticidal activity [88]. Introducing a substituted phenyl ring into osthole could enhance its insecticidal activity. Its activity sequence was that *para*-substituted compounds were better than *meta*-substituted compounds; electron-donating compounds were better than electron-withdrawing compounds [90]. Hydrazone derivative **53** (Fig. S7) prepared with fraxinellone as the lead also had certain insecticidal activity at a concentration of 1 mg/L, the lethality rate of compound **53** to *M. separata* was 76% [91].

To continue to search for high-activity natural product insecticides, a high-activity compound **54** (Fig. S8 in Supporting information) could be obtained by introducing hydrazone into quinoline, and its control effect against *S. litura* was 100% at a concentration of 1 mg/L [92]. A series of hydrazone derivatives with good to excellent activity against *T. cinnabarinus* were obtained by introducing thiourea, urea, and acyl thiourea into the 7-position of the natural product camptothecin [93]. The representative compound **55** ( $LC_{50} = 0.00761$  mmol/L) (Fig. S8) showed better activity than the control camptothecin ( $LC_{50} = 0.19719$  mmol/L) [93]. The author also developed 3D-QSAR models of these derivatives, which proved that the size of substituents played an important role in the activity of camptothecin derivatives modified at the 7-position [93]. In addition, the genipin derivative **56** (Fig. S8) synthesized by Wang and his colleagues had insecticidal activities against *M. separata*, *C. bollworm*, and *C. borer* [94]. The new monocyclic  $\beta$ -lactam extracted from the natural product gallic acid was spliced with hydrazone fragments to obtain derivative **57** (Fig. S8) with strong insecticidal activity. It provides specific ideas for such derivatives as insecticides [95].

### 3. Antibacterial and antifungal activity

Bacterial and fungal diseases of plants have always been one of the important causes of crop yield reduction, therefore causing huge economic losses worldwide [96]. In recent years, traditional fungicides used to control bacterial and fungal diseases in plants have posed a threat to ecosystems, killing target bacteria and fungi and affecting beneficial living systems [97]. Therefore, developing novel and promising antibacterial and antifungal drugs remains an urgent task. For a long time, hydrazone derivatives have been widely used to control plant bacterial and fungal diseases and have

been produced commercially for many years [98]. Benquinox and ferimzone are important representatives of commercial fungicides containing hydrazone.

As mentioned above, natural product pesticides have long been a research hotspot for pesticide workers and are widely used to control bacterial and fungal diseases [99]. Wang and coworkers devoted their research to natural products containing hydrazone structures for many years and discovered a batch of indole alkaloids, toad alkaloids, and echinin alkaloid derivatives with antifungal and antiviral activity (The antiviral activity is described in detail in Section 4) [100–105]. For example, they took indole as the leader and introduced hydrazone structures to synthesize hundreds of hydrazone derivatives with broad-spectrum biological activities (Fig. S9 in Supporting information) and applied them to antifungal, antiviral, and insecticidal aspects. Among them, derivative **58** (Fig. S9) had good antifungal activities against 14 kinds of fungi with inhibitory activity ranging from 62.2% to 97.0% at a concentration of 50 mg/L [100]. The authors then constructed derivatives **59**, **60** and **61** (Fig. S9) based on derivative **58**, although their spectrum of antifungal activity was not greatly improved. However, its structure was novel, providing ideas for developing new fungicides (more details for structure-activity relationship analysis of compounds **59–61** see Section S2 in Supporting information). The aromatic aldehyde-containing compound **62** (Fig. S9) showed a strong inhibitory effect against both *A. solani* (67%, 50 mg/L) and *S. sclerotiorum* (87%, 50 mg/L). The antifungal activity was better than that of the control chlorothalonil (<50%, 50 mg/L) [103]. They tried to change indole alkaloids into toad alkaloids and echinopsine with important biological activities and designed and synthesized toad alkaloid derivatives **63** and echinopsine derivatives **64** (Fig. S9) with hydrazone structures. Derivative **63** had good antifungal activity against *S. sclerotiorum*, *R. cerealis*, and *B. cinerea* (100%, 98%, 71%, 50 mg/L) and was superior to the control chlorothalonil (93%, 45%, 19%, 50 mg/L) [104]. Compound **64** had high antifungal activities against *P. piricola* and *S. sclerotiorum*, and the antifungal activity of compound **65** (Fig. S9) containing a substituted phenyl ring was relatively higher than that of the compound containing a heterocyclic ring [105]. In addition, by integrating the lindenone and hydrazone structures into one molecule, a series of *N*-aminomaleimide derivatives **66** (Fig. S9) with good antifungal activity can also be obtained [106]. The antifungal activity of most compounds against phytopathogenic fungi was much higher than that of precursor lindanone. Among them, compound **67** (Fig. S9) showed broad-spectrum antifungal activities, and its inhibition rate against 11 plant pathogenic fungi, such as *R. cerealis*, was more than 50% [106]. The new hydrazone derivative **68** (Fig. S9, SAR analysis see Section S2) containing the natural bioactive sesquiterpene carabrone structure also has a good control effect on *B. cinerea* and *C. arachidicola* [107]. In general, introducing chlorine or bromine atoms into the substituents could enhance the antifungal activity of carrageenan ketone hydrazone derivatives *in vitro* and *in vivo* [107]. Compound **69** (Fig. S9), containing an indole group, had good bactericidal activities against three tested bacteria (*Xanthomonas axonopodis* pv. *citri*, (*Xac*); *Xanthomonas oryzae* pv. *oryzae*, (*Xoo*); *Ralstonia solanacearum*, (*Rs*)) and was superior to the commercial bactericides bismethiazol and thiodiazole copper [108]. Recently, the small molecular compound **70** (Fig. S9) designed by Yu with the natural product chromone as the lead compound could be regarded as an effective candidate for bactericide [109]. It had excellent inhibitory activities against *Xoo*, *Xoc* and *Xac* (half maximal effective concentration ( $EC_{50}$ ) values were 8.0, 12.0 and 10.0 mg/L, respectively), which was significantly better than that of commercial bactericide ( $EC_{50}$  values were 84.0, 151.0 and 145.0 mg/L, respectively) [109].

In addition, by linking phenyl groups with different substituents to various heterocycles (such as naphthyridine, quinoxaline,

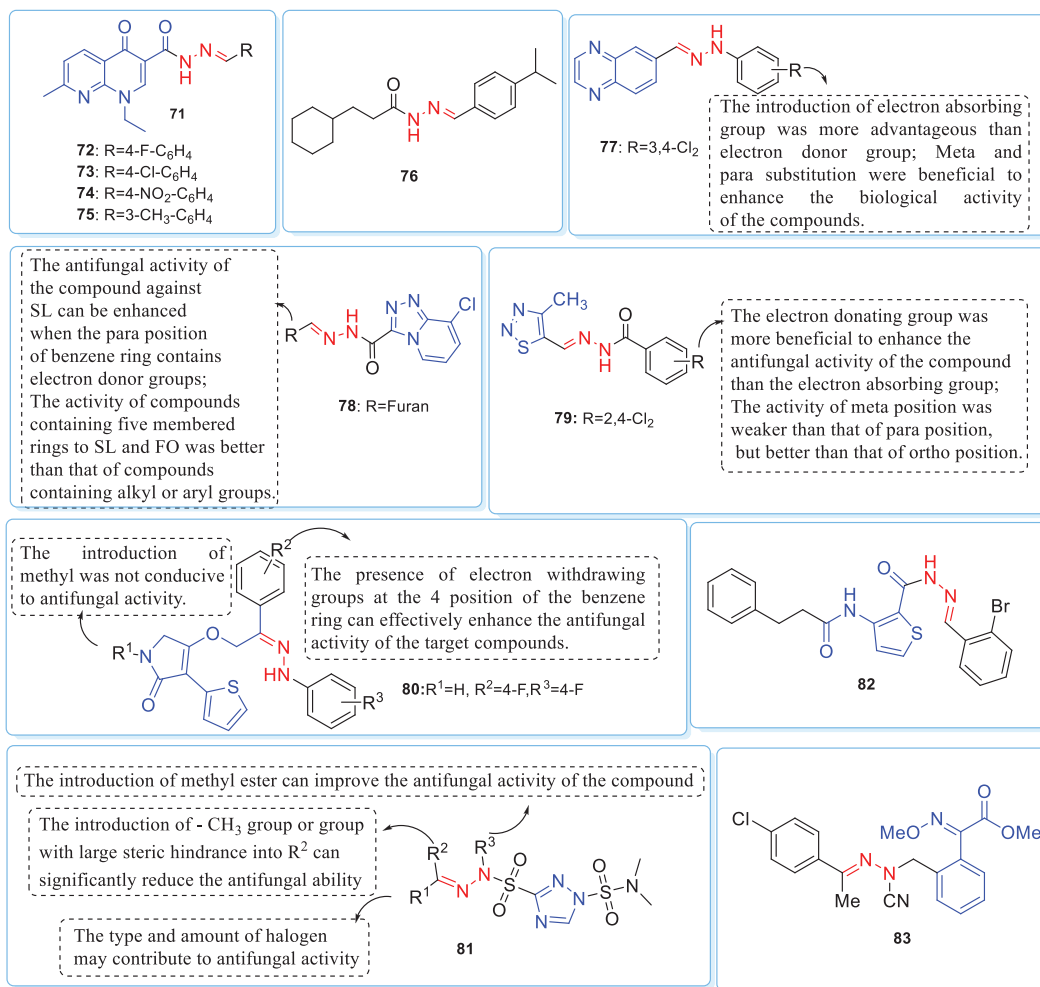


Fig. 4. The structures and SAR of hydrazone derivatives **71** to **83**.

triazolopyridine, thiadiazole) via hydrazones (Fig. 4), numerous bioactive molecules with excellent inhibitory activity against plant bacterial and fungal diseases were obtained. For example, hydrazone was used as a linker to connect the substituted phenyl group to naphthyridine to get a series of derivatives **71** (Fig. 4). Derivatives **71** possessed good activity against four pathogenic fungi with good inhibitory activities. Fluorine-substituted derivatives were more potent than chloro- and bromo-substituted substituents, regardless of their position (e.g., fluorine-substituted compound **72** was more antifungal than chlorine-substituted compound **73**, more details see Section S2) [110]; in the para position hydrazone derivatives with the electron-withdrawing nitro group and the electron-donating methyl group at *meta*-position have significant antifungal activity (the nitro-substituted compound **74** and methyl-substituted compound **75** have EC<sub>50</sub> values of 70.1 mg/L, 57.6 mg/L) [110]. When the linked small molecule was replaced with the cyclohexyl group, compound **76** (Fig. 4) had better inhibitory activities against *Phomopsis obscurans* (*P. obscurans*) and *Phomopsis viticola* (*P. viticola*) [111]. Quinoxaline hydrazone derivatives have been found to be highly effective in controlling *R. solani*. In particular, the electron-withdrawing substituent (chlorine) compound **77** (Fig. 4) has excellent antifungal activity against *Rhizoctonia solani*, and its EC<sub>50</sub> value was 0.1 mg/L, which was significantly better than that of the fungicide Carbendazim (EC<sub>50</sub> = 1.4 mg/L), although its fungicidal activity spectrum was narrow [112]. The hydrazone fragment was integrated into triazolopyridine to give **78** (Fig. 4),

which had good inhibitory effects against other types of fungi (such as *Stemphylium lycopersici* (*S. lycopersici*) and *F. oxysporum* sp.) [113]. Further SARs analysis showed that the antifungal activity of the compound against *S. lycopersici* could be enhanced when the benzene ring contained an electron-donating group at the para position [113]. Recently, Zhang has explored the potential of hydrazones as connectors between small molecules of thiadiazoles and phenyl groups to create a portfolio of derivatives that boast a comprehensive antifungal activity. In particular, compound **79** (Fig. 4) had good inhibitory activities against *Valsa mali* (*V. mali*), *B. cinerea*, *Pythium aphanidermatum* (*P. aphanidermatum*), *R. solani*, *F. moniliforme* and *A. solani*. Its EC<sub>50</sub> values were 8.2, 24.4, 15.8, 40.5, 41.4 and 34.1 mg/L, respectively [114]. In addition, the authors found that the position of the substituent R on the benzene ring plays an important role in the antifungal activity [114].

As an attractive nitrogen-containing heterocyclic compound, tetramine acid has excellent properties, such as good environmental compatibility and easy synthesis [115]. Based on the excellent characteristics of tetramines, compound **80** (Fig. 4) obtained by introducing a hydrazone fragment could effectively inhibit plant pathogenic fungi such as *F. graminearum*, *R. solani* and *Colletotrichum capsici* (*C. capsici*) [116], with EC<sub>50</sub> values of 1.2, 6.0, 6.1 mg/L, which was better than or similar to that of the control drug drazoxolon (EC<sub>50</sub> values were 1.7, 19.4, 3.5 mg/L, respectively) [116]. In addition, triazolesulfonyl hydrazone small molecules **81** (Fig. 4) containing hydrazone fragments had excellent control

effects against cucumber downy mildew [117]. Its SARs is shown in Fig. 4. Compound **82** (Fig. 4) had excellent anti-Xoo activity, and its EC<sub>50</sub> value was 4.7 mg/L, which was significantly better than that of the commercial fungicides mectazole (EC<sub>50</sub> = 66.8 mg/L) and copper thiophanate (EC<sub>50</sub> = 72.3 mg/L) [118]. Trioxystrobin is a commercial fungicide with high efficiency, broad-spectrum, resistance to rain erosion, and long-lasting effects [119]. Inspired by this, Jia took it as a guide and changed the linking oxime to hydrazone to obtain a series of compound **83** (Fig. 4) with a wider spectrum of fungicidal activity, among which compounds **83** were used in the field test of the same application dose against cucumber powdery mildew and rice blast fungus [120]. Its inhibitory activity was comparable to or better than the commercial fungicides tricoxystrobin and procloraz, which can be used as candidate drugs for further study [120].

To find fungicides with better antifungal activity, researchers used the principle of substructure splicing to splice hydrazone and thiazole rings to obtain compounds **84**, **85**, **86** (Fig. S10 in Supporting information) with antifungal activity. At a concentration of 100 mg/L, the inhibitory rate of derivative **84** on *Botrytis cinereapers* was 91%, equivalent to difenoconazole (95%) [121]. Compound **85** showed good fungal activities against *S. sclerotiorum*, the inhibition rate was mostly above 90% at 500 mg/L [122]. Compound **86** also had a good control effect on *B. cinereapers* and *R. solani* [123]. Pyrazole-containing hydrazone derivatives **87**, **88** (Fig. S10) also have some antifungal activity [124,125]. The hydrazone derivative **89** (Fig. S10) containing a pyrimidine structure can be used as a fungicide. At a concentration of 50 mg/L, the inhibition rate of some compounds was higher than 90%. It can also effectively alleviate the phytotoxicity of amide herbicides such as metolachlor sperm on crops and can be used as an herbicide safener [126]. Using isatoic anhydride as the starting material, a series of quinazolinone derivatives **90** (Fig. S10) containing hydrazone fragments were synthesized. It showed good inhibitory activity, and some compounds had better antifungal activity than the control drugs bismertiazol and thiophanate copper [127]. Compound **91** (Fig. S10) showed strong activity against *F. oxysporum*, and *S. fuliginea*. The mechanism of action study indicated that this compound could induce the expression of the specific marker genes *LOX<sub>1</sub>* and *Cs-AOS<sub>2</sub>* of the jasmonic acid signaling pathway, therefore triggering the defense resistance of plants [128]. In addition, splicing substituted phenyl groups with hydrazones can obtain satisfactory hydrazone derivatives. For example, the hydrazone derivative **92** (Fig. S10) reported by Liu has a strong inhibitory effect on wheat stripe rust. The minimum inhibitory concentration was 150 mg/L to 420 mg/L, which can be used as a pesticide lead compound for further development [129]. Kaji has invented a series of hydrazones **93** (Fig. S10), which had good pest control activity, especially broad bactericidal activity. It has a good control effect on *B. cinerea* and so on [130]. The derivative **94** (Fig. S10) invented by Young also has broad-spectrum fungal activity, inhibiting phytopathogenic fungi and fungal pathogens of mammals, including humans. In particular, it had strong inhibitory activity against phytopathogenic fungi [131].

#### 4. Antiviral activity

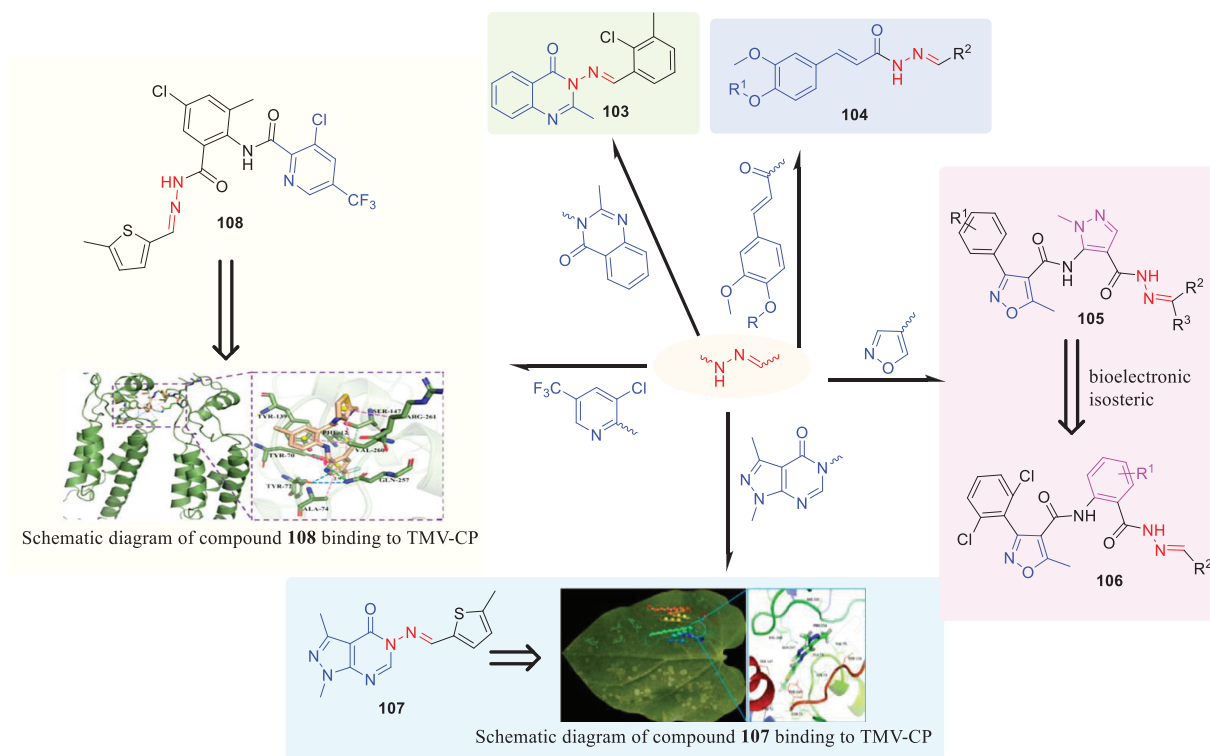
Plant virus disease, called “plant cancer”, is the second largest plant disease after plant fungal disease [132], which has caused great harm to agriculture [133]. However, ningnanmycin and ribavirin, the main pesticides used to control plant virus diseases, were ineffective in the field [134]. Therefore, it is of great significance to develop new antiviral drugs with high efficiency and environmental protection. Through a literature investigation, it was found that the inhibitory effect of derivatives containing hydrazone structures on plant virus diseases cannot be ignored [135]. How-

ever, there were no reports of commercial antiviral agents in plant virus resistance.

As we mentioned earlier, Wang discovered a group of derivatives with novel structures and broad biological activities, among which the antiviral activity exhibited the best performance. For example, the plant-derived natural product carboline alkaloid was used as the guide. A hydrazone was introduced as a bridge to connect with different substituted aromatic groups to obtain a series of hydrazone derivatives with novel structures. Among them, the control effect of compound **95** (Fig. S11 in Supporting information) against TMV disease was as high as 100% under the dosage of 100 g/hm<sup>2</sup> with a simple synthesis method, low toxicity to rats, and good application prospects [100,136]. Based on derivative **95**, four chiral isomers **95a**, **95b**, **95c** and **95d** (Fig. S11) were constructed, and their anti-TMV activity was systematically studied [137]. The EC<sub>50</sub> values of the four chiral isomers were 203, 180, 108, and 200 mg/L, respectively, which were significantly better than that of ningnanmycin (392 mg/L), which laid a good foundation for the research and development of chiral anti-plant virus drugs. Then, a piperazinone fragment was inserted between the carboline alkaloid and the hydrazone, resulting in derivative **96** (Fig. S11) with excellent anti-TMV activity [103].

Additionally, four chiral isomers **96a**, **96b**, **96c** and **96d** (Fig. S11), were constructed to consolidate the research and development of chiral anti-plant virus agents. It was proven that the spatial conformation was the most important factor regulating antiviral activities, providing a reference for the best possible configuration for the molecule to interact with its target protein. If the six-membered ring in derivative **96** was cut off, derivative **97** (Fig. S11) with antiviral activity could be obtained [138], but its antiviral activity had not been greatly improved. In addition, based on derivative **95**, the six-membered ring was changed into a five-membered ring. A small modification could also obtain derivative **98** (Fig. S11) with antiviral activity equivalent to that of derivative **95** [101,139]. The authors found the introduction of electron-withdrawing groups into the benzene ring was beneficial to the anti-TMV activity; the introduction of sterically hindered groups on the benzene ring can also significantly improve the antiviral activity of the compound (For more details, see Section S2). Wang's team used acyl hydrazone as a linker to modify natural active molecules such as matrine, toad alkaloid, and streptomycin alkaloid and obtained compounds with excellent TMV control effects. For example, modification of the active molecule matrine with electron-withdrawing phenyl groups can yield compound **99** (Fig. S12 in Supporting information) with much higher anti-TMV activity than matrine and the commercial anti-plant virus agent ribavirin. Interestingly, compound **99** was further modified to give compound **100** (Fig. S12). This type of matrine hydrazone compound showed better anti-TMV activity than **99** [140]. Additionally, compounds **101** and **102** (Fig. S12) with excellent anti-TMV activity could also be obtained if the active molecules linked in compound **100** were replaced with toad alkaloids and streptomycin alkaloids. Their mechanism of action was preliminarily studied, and it was found that derivatives **101** and **102** exerted excellent antiviral effects by inhibiting the assembly of TMV particles by interacting with TMV CP [104,141].

Song *et al.* used a hydrazone as a linker to diversify one side of the Schiff base and introduce an active group of quinazoline on the other side to obtain the compound **103** (Fig. 5). It had better antiviral activity by inducing the upregulation of *PR-1a* and *PR-5* genes, thereby enhancing the activity of certain defense enzymes and inhibiting the proliferation and movement of viruses [142]. If a pyrazole ring is used to replace the quinazoline ring in compound **103** and a modified isoxazole ring is inserted simultaneously, compound **104** (Fig. 5) has a good control effect against TMV can also be obtained [143]. Then, on this basis, the author changed the



**Fig. 5.** Hydrazone-containing derivatives (**103–108**) with antiviral activity. Reproduced with permission [135]. Copyright 2019, American Chemical Society. Reproduced with permission [146]. Copyright 2018, Elsevier Science Ltd.

pyrazole heterocyclic ring into a benzene ring through biological isostatic discharge and obtained derivative **105** (Fig. 5) with better activity, which showed a good control effect against TMV and cucumber mosaic virus (CMV), for more details of SAR analysis see Section S2 [144]. In addition, the introduction of ferulic acid into the hydrazone fragment yielded compound **106** (Fig. 5) with excellent inactivation activity. Studies have shown that such derivatives exhibit antiviral effects due to their interaction with tobacco mosaic virus coat protein (TMV-CP) [145]. Based on the active substructure of "pyrazolopyrimidine", Wu and coworkers obtained a series of pyrazolopyrimidine compounds through hydrazone as a bridge. Compound **107** (Fig. 5), which had significantly better anti-plant virus activity than the commercial drugs ningnamycin and ribavirin, was screened. It was found that the active compound **107** could prevent the self-assembly of TMV virus particles by interacting with TMV-CP subunits such as hydrogen bonds,  $\pi$ -sulfur, and  $\pi$ -alkyl and ultimately showed an antiviral effect [146]. By integrating trifluoromethyl pyridine, phthalimide, and hydrazone fragments, compounds with excellent anti-TMV activity could also be screened, and their antiviral activity spectrum was wider (it also shows excellent antiviral activity against CMV). In particular, the curative activity of compound **108** (Fig. 5) against TMV was nearly 5 times that of the commercial drug ningnamycin (the  $EC_{50}$  of the curative activity of compound **108** was 75 mg/L, while the  $EC_{50}$  of ningnamycin under the same conditions was 362 mg/L). Its inactivation activity was comparable to that of ningnamycin. Therefore, we explored the mechanism of action of compound **108** in detail and found that it obtained anti-plant virus activity by acting on the key binding site between the two subunits of TMV-CP and affecting the self-assembly of the TMV virus [135].

## 5. Herbicidal activity

In recent years, reports of hydrazone derivatives in herbicides have decreased, and hydrazone fragments are still an important

framework for the discovery of new herbicides. For example, a series of acyl hydrazone derivatives **109** (Fig. S13 in Supporting information) could be obtained by combining diaryl ethers with hydrazone fragments, which had excellent inhibitory effects on rape grass and barnyard grass [147]. In addition, the introduction of active groups such as  $\alpha$ -pinene and camphoric acid on the hydrazone fragment could also obtain compounds **110** and **111** (Fig. S13) with better herbicidal activity [148,149]. In 2015, František found that compound **112** (Fig. S13) has an excellent inhibitory effect on spinach and clarified that the high activity of compound **112** was related to the presence of the thienyl group in this compound because the free electron pair of sulfur in the thiophene moiety could interact with the components of the photosynthetic apparatus through hydrogen bonding to exert an excellent inhibitory effect. In addition, EPR spectra showed that the active compound **112** had a good inhibitory effect on the photosynthesis of spinach chloroplasts, which might be related to the interaction of aromatic amino acids in photosynthetic proteins [150]. Hydrazone derivatives **113** (Fig. S13) containing chlorobenzopyrazine structures also had certain herbicidal activity [151].

## 6. Summary and outlook

Based on the abovementioned facts, we found that the hydrazone structure is a promising chemically active component of pesticides. It can combine with additional donor sites ( $C=O$ ,  $O=S=O$ ) to form a stable bond energy with the target, therefore having high biological activity. As mentioned above, compound **107** can interact with TMV-CP, therefore preventing the self-assembly of TMV virus particles and finally achieving an antiviral effect. Therefore, the structures of the acyl hydrazone and sulfonyl hydrazone have become the research focus of pesticide workers. In addition, acyl hydrazone compounds contain  $-CONHN=CH-$  groups, which are formed by the condensation of aldehydes or ketones with hydrazide. Its chemical structure determines that it not only reduces

the toxicity of the  $-NH_2$  group in the hydrazone structure to the organism but also contains oxygen atoms and nitrogen atoms to participate in the formation of hydrogen bonds in the organism, enhancing the affinity between receptors and making acyl hydrazone compounds have better biological activity. The above literature reports found that surprising active derivatives can usually be obtained by introducing functional groups such as natural products (cholesterol, indole, chromone, etc.), substituted benzene rings, and heterocycles into hydrazone structures. In addition, the introduction of electron-withdrawing groups can also highlight the biological activity of the compounds. In addition, although there are many reports about hydrazone structures in insecticidal and antifungal activities, some promising candidate compounds have been found (such as benzophenone hydrazone derivatives with high insecticidal activity against Lepidoptera pests). However, most studies have only carried out simple activity tests and structure-activity relationship research on hydrazone derivatives but have not carried out further research on active compounds. Therefore, the mechanism (or target) of most hydrazone derivatives in insecticidal and antibacterial activities is still unclear, which limits the in-depth optimization of their structures to some extent.

To date, although the application of hydrazone derivatives in antiviruses was discovered late, there are no commercial varieties. However, molecular docking, MST, transmission electron microscopy, and related defense enzyme tests have preliminarily clarified the interaction between active compounds and targets. To some extent, it promoted the development of hydrazone derivatives in antiviruses. It is not difficult to find that the study of the structure-activity relationship is still an important means to optimize hydrazone compounds. The quantitative structure-activity relationship study will provide effective information for further structural modification and improve the discovery efficiency of active compounds. It will be a new research trend to study and analyze the interaction between small molecule drugs and targets by using bioinformatics, molecular biology, structural biology, and chemical biology methods and to build a research system of high-activity molecular targets and action models.

### 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.

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### Supplementary materials

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