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Review

Trifluoromethylpyridine: An Important Active Fragment for the Discovery of New Pesticides

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ABSTRACT: Trifluoromethylpyridine (TFMP) is a biologically active fragment formed by connecting trifluoromethyl and pyridine ring. As a result of its unique physical and chemical properties and outstanding biological activity, a variety of pesticide compounds with the TFMP fragment have been discovered and marketed and have played important roles in crop protection research. It is therefore a timely and valuable task to summarize the rationality on how to create new molecules containing TFMP fragments based on the structure−activity relationships, design mentality, and potential mechanism. This review gives a brief summary on the pesticides containing TFMP fragments in the past 5 years and introduces the latest progress of our group in this field. The aim is to provide readers with a convenient route to touch this topic and hopefully serve some educational purpose for graduate students as well.

KEYWORDS: *trifluoromethylpyridine, biological activity, crop protection, pesticide*

1. INTRODUCTION

In organic chemistry and medicinal research, the design, synthesis, and evaluation of drug molecules with a wide range of biological activities are the objects of continuous efforts from scientists. Active fragments, as a key component of chemical drug structures, have been widely used in the fields of drug derivatization, agrochemical product innovation, target compound designs, and characterization of structure−bioactivity relationships (SARs).[1,2] Therefore, the identification and utilization of bioactive fragments are of great significance in exploring new drug structures, optimizing drug efficacies, and reducing research and development costs. The special structure of trifluoromethylpyridine (TFMP; Figure 1) has received increasing attention in recent years as a result of its simple operations in the synthesis and broad-scope bioactivities against various plant pests.

Trifluoromethyl possesses unique properties, including electronic effects, hydrogen-like simulation effects, and fat-soluble penetration effects. These properties can greatly affect the conformation, biomolecular affinity, and metabolism of the compounds and render them less toxic with novel biological activities. It is therefore widely used in the field of pesticide chemistry.[3−5] In the field of crop protection, TFMP is the most widely used fluorine-containing heterocycle in fluorine-containing pesticides. It has a wide range of agrichemical applications, such as insecticidal,[6,7] fungicidal,[8] and herbicidal[9] agents. To date, about 30 launched pesticides contain the moiety of TFMP. Some of the TFMP-derived pesticides are shown in Figure 2.

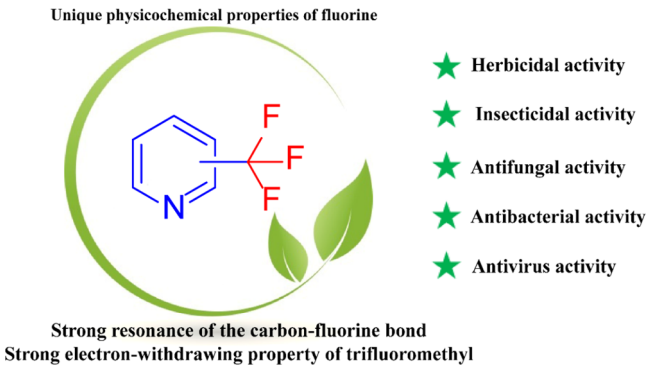

Figure 1. TFMP and its biological activity.

Although reviews on the synthetic approaches and biological applications of TFMP derivatives have been documented, they mainly focused on the synthesis and related characteristics of existing varieties.[5,10] To the best of our knowledge, the design mentality and relationship between the structures of TFMP derivatives and their biological activities have not yet been summarized. Herein, we summarize the new progresses in the development of the bioactive molecules containing TFMP fragments according to the design mentality, SARs, and mechanism. A brief introduction of the strategies used in developing novel TFMP-derived pesticides is also given to hopefully serve some educational purpose for new players and graduate students coming into this research field as well.

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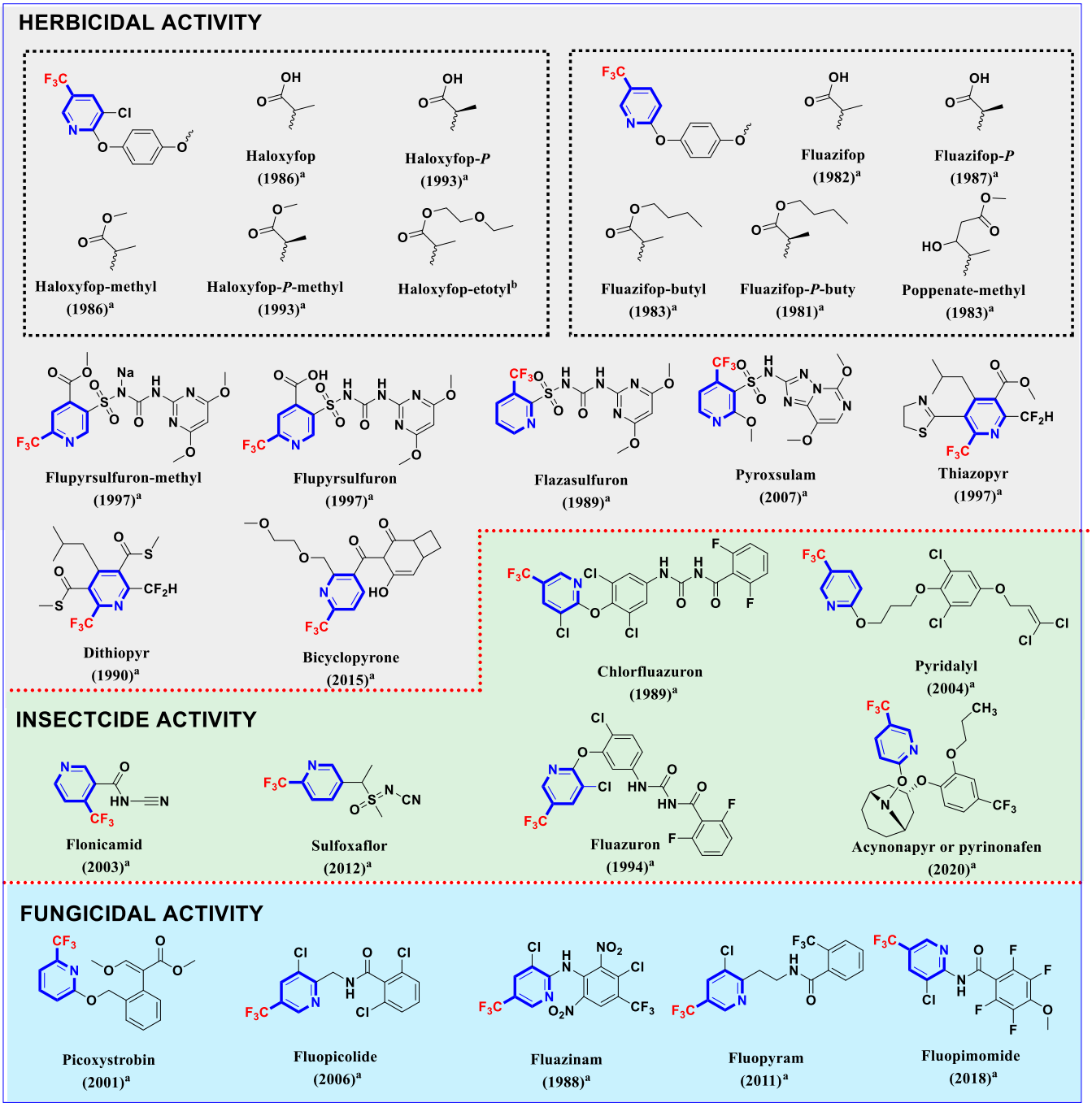

Figure 2. Selected commercial pesticides containing TFMP. [a]Year of introduction, [b]Year of introduction not available.

2. DATA COLLECTION

Pesticides are compounds widely used in agriculture to eliminate weeds, insects, and pathogenic microorganisms.[11] To date, herbicides have accounted for approximately two-thirds of the marketed pesticides bearing the TFMP fragments; fungicides and insecticides have approximately accounted for the remaining one-third of them. The innovation for pesticide frameworks is one of the important methods to reduce pesticide resistance and to effectively prevent plant diseases.[12] A number of unprecedented molecules containing TFMP fragments have been discovered with good agricultural biological activities via pesticide framework innovation strategies.[13−15]

We used SciFinder and the European Patent Office (EPO) to search for relevant documents from 2010 to August 2021 with "synthesis", "trifluoromethylpyridine", "herbicidal activity", "insecticidal activity", "antifungal activity", "antibacterial activity", and "antiviral activity" used as the keywords, separately. The literature statistics on the activity of TFMP-containing compounds in the past 10 years are shown in Figure 3. In the past 10 years, researchers have been focused on the herbicidal and insecticidal activities of TFMP derivatives, with the related publications accounted for the majority of the annual studies. Investigations regarding antifungal, antibacterial, and antiviral bioactivities have also been carried out with TFMP derivatives, although fewer reports have been documented within these directions. From 2010 to 2014, the

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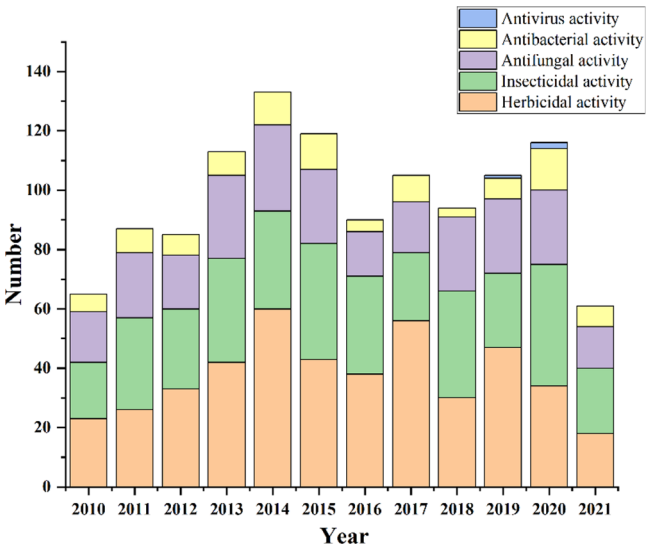

Figure 3. Publication of TFMP compounds discovered on SciFinder and the EPO from 2010 to August 2021. The literature search used "trifluoromethylpyridine structure", "herbicide", "insecticide", and "fungicide" as keywords. The file types are journaled research papers and patents.

related reports on herbicidal activity in the literature show an increasing trend year by year, reaching the highest in the year 2014 with 60 publications (Figure 3). Studies on insecticidal activities of TFMP derivatives have also attracted more and more attention, with 41 publications reported in 2020 (Figure 3). Reports of antifungal and antibacterial activities of this type of molecule have also shown a gradual increase. Only limited reports have been published regarding the antiviral bioactivities of small molecules containing TFMP moieties. In this mini review, we have chosen the representative work of the latest 5 years bearing this active fragment to expound the progress of TFMP derivatives and highlight the importance for the active fragment in pesticide innovation.

3. BIOLOGICAL ACTIVITIES OF TFMP DERIVATIVES

3.1. Herbicidal Activity. It has been proven that TFMP can provide promising herbicide activities by the diversity of commercially available pesticides containing TFMP fragments. In the past 5 years, Syngenta[16−21] has reported several types of herbicidal active compounds, as summarized in Figure 4. In these cases, TFMPs with different substitution patterns are connected directly or indirectly to various mioties (such as cyclopentane-1,3-dione, pyrrolidin-2-one, imidazolidine, tetrazole, pyrazole, imidazole, pyridazine, pyrimidine, etc.) (Figure 4), to give a number of bioactive molecules with good inhibitors or control activities against a broad scope of weeds. For instance, the TFMP moiety can be linked with phenylpyridazinone via a ethylidene to give compound **1**,[16] and it showed excellent postemergence activity (the control rate is over 90% at 60 g/ha) against multiple broadleaf weeds. Although there was a similar phenyl heterocycle, the linker between this group and TFMP was changed to ethylcyclopentane-1,3-dione, and the resulting compound **2** showed excellent inhibitory activity against gramineous weeds, including *Alopecurus myosuroides*, *Avena fatua*, *Lolium perenne*, and *Echinochloa crusgalli* at 50 g/ha in both pre-emergence and postemergence tests.[17] While the TFMP structures were directly connected with pyrrolidin-2-one or imidazolidine, the obtained corresponding compounds are also found to exhibit good herbicidal activities. Among them, compounds **3** and **4** were able to thoroughly remove the herbs of *Amaranthus retroflexus*, *Abutilon theophrasti*, *Setaria faberi*, and *Echinochloa crusgalli*.[18,19] Moreover, introduction of both the heterocycle (pyrazole, triazole, etc.) and amide with heterocycle could broaden the weeding range; for example, compounds **5** and **6** could damage both gramineous weeds and broad-leaved weeds before and after emergence at 500 g/ha. Furthermore, phenoxyacetic (**7**) or phenoxyacetamide (**8**) containing the moiety of TFMP also demonstrated herbicidal activity (postemergence) toward *Amaranth*, *Chenopodium*, and *Setaria* spp. at 16 g/ha. Although the SARs and mechanism for herbicidal activity of these TFMP derivatives are not clear, the data indicated that TFMP could be used as a basic active fragment for the discovery of a herbicide.

On the basis of the SAR studies, Huo et al.[24,25] demonstrated that the introduction of TFMP to give the compounds **9** and **10** can dramatically increase their herbicidal activities and their herbicidal spectrum (Figure 5) and can be used as transketolase inhibitors.[25] Liu et al. designed and synthesized a series of TFMP-containing compounds through intermediate derivatization methods.[26] The structure of sulfonamide was introduced to the skeleton of TFMP−benzene to give compounds **11a−11i** (Figure 5) with significant herbicidal activity against *Abutilon theophrasti* Medic. and *Zinnia elegans* Jacq. at 7.5 g/ha of active ingredient. Particularly, compound **11b** displayed a wide herbicidal spectrum and could be regarded as a potential candidate. SAR analysis revealed that the herbicidal activity of the compounds bearing *N*-methyl groups is greater than that of the compound bearing a free NH group. Switching the sulfonamide groups of the compound **11** into an easter group resulted in drops of the herbicidal activity. As for the R^2 group, the increases of the chain length (or ring) are also unfavorable to herbicidal activity. More recently, Fu and partners[27] proposed that compounds **12a** and **12b** (IC_{50} values were 2.238 and 1.423 μM, respectively) can be regarded as effective candidates. They observed that the substitution of a trifluoromethyl group at the *para* position was critical to the herbicidal bioactivity of the molecule.[27] Furthermore, compounds **13a−13h** (Figure 5) can be used as protoporphyrinogen oxidase (PPO) inhibitors and were found to result in prominent herbicidal activities. Significantly, $-CF_3$ on the pyridine rings could enhance the activity on PPO.

3.2. Insecticidal Activity. TFMP derivatives have also been used by Syngenta as effective insecticides, as summarized in Figure 6. The general structures of the TFMP derivatives in insecticides can be divided into four parts: A, B, C, and D (Figure 6). Part A is the TFMP fragment with a variety of substitutes (such as ethylsulfonyl, ethylthio, chlorine atom, and cyclopropane) installed on the different positions of the ring structures. Part B is the linear bridging part, consisting of both heteroatoms and carbon chains. Both parts C and D are heterocyclic structures involving both aromatic rings and nonaromatic rings (such as thiazole, thiadiazole, imidazole, pyrazole, etc.). Compounds **14−18** (not commercialized) are some representative insecticides developed by Syngenta[30−38] with both trifluoromethyl groups and sulfonyl groups introduced into their ring substituents. The synthesis of compounds **14** and **15**[32,33] involves steps of aromatic cross-couple reactions that directly connect the three aromatic fragments in stepwise species. In these compounds, both target

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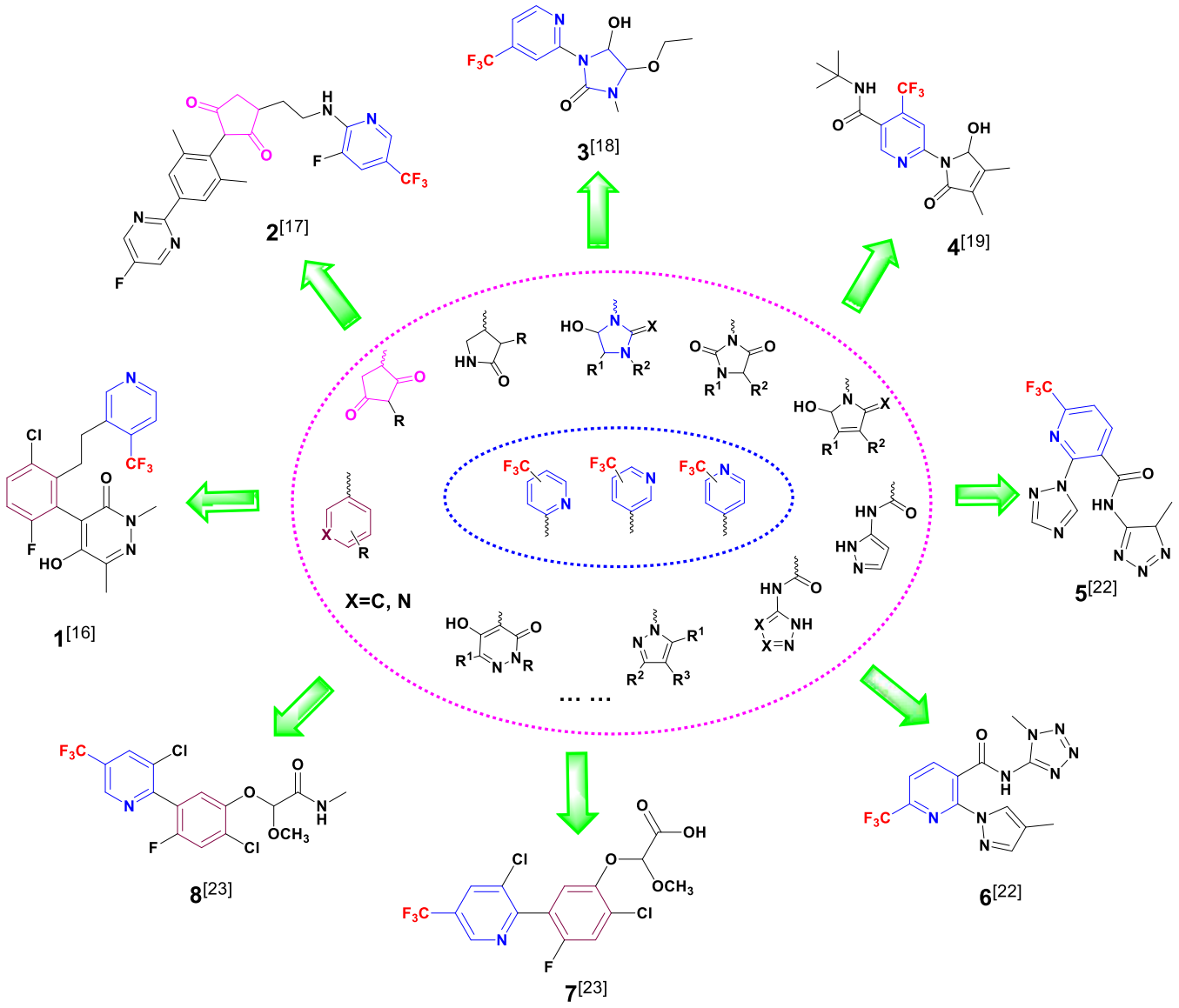

Figure 4. Derivatives with herbicidal activities containing TFMP fragments from Syngenta.

insects and bioactivities of compounds varied when changing the substitution position of the trifluoromethyl group on the pyrazole ring of the insecticide structures. All of these molecules possess more than 80% insecticidal activities against *Spooptera iittoralis*, *Plutella xvlostella*, *Diabrotica balteata*, *Mvzus persicae*, and *Euschistus hems* at 200 mg/L. The trifluoromethyl pyridoimidazolyl group was directly connected to the TFMP fragment with a 2-substituent of ethylsulfonyl to yield compounds **16**−**18**; all of them showed good insecticidal activity.[33] In addition, 1-cyanocyclopropyl-substituted TFMP amide derivatives with a *N*-bis-heterocyclic ethyl have good and broad insecticidal activity.[34,37,38] For example, compound **19** has more than 80% insecticidal activity against a wide range of insects, including Lepidoptera (*Plutella xvlostella*, *Chilo suppressalis*, and *Spodoptera iittoralis*), Coleoptera (*Diabrotica balteata*), Hemiptera (*Mvzus persicae* and *Euschistus heros*), Thysanoptera (*Frankliniella occidentalis*), etc. It provides a useful skeleton with broad activity for optimizing and discovering the novel TFMP amide insecticide.

In 2016, Shi et al.[39] integrated a 5-trifluoromethylpyridyl unit into the scaffold of fenpyridyl for the first time to yield some TFMP derivatives, which show moderate to good insecticidal activities against *Tetranychus cinnabarinus*, *Plutella xylostella*, and *Aphis craccivora*. Although their activity is not satisfactory, some innovations have been made in the structure to obtain a novel insecticidal active skeleton. Interestingly, using piperazine as the linker between TFMP and substituted phenoxy ether could result in novel structures with excellent nematicidal activity. This type of TFMP-containing piperazine derivative showed broad-spectrum insecticidal activity against not only some kinds of nematodes but also armyworms, *Aphis medicagini*, and rice planthoppers. Besides, the compound with Cl at the R^1 group (**20**; Figure 7) exhibited higher activity than the H atom at the R^1 group, and the R^2 group seems to be related to the selectivity of insecticidal activity.[40] More recently, Song and co-workers[41] incorporated a 1,3,4-oxadiazole sulfide fragment with TFMP to afford the disulfide compound with excellent nematicidal activities (Figure 7) as avermectin.[41] SAR investigations indicated that methyl could enhance the activity more than ethyl.

Inspired by the commercial insecticide chlorantraniliprole, our group spliced the active fragments of 3-chloropyridin-2-yl-

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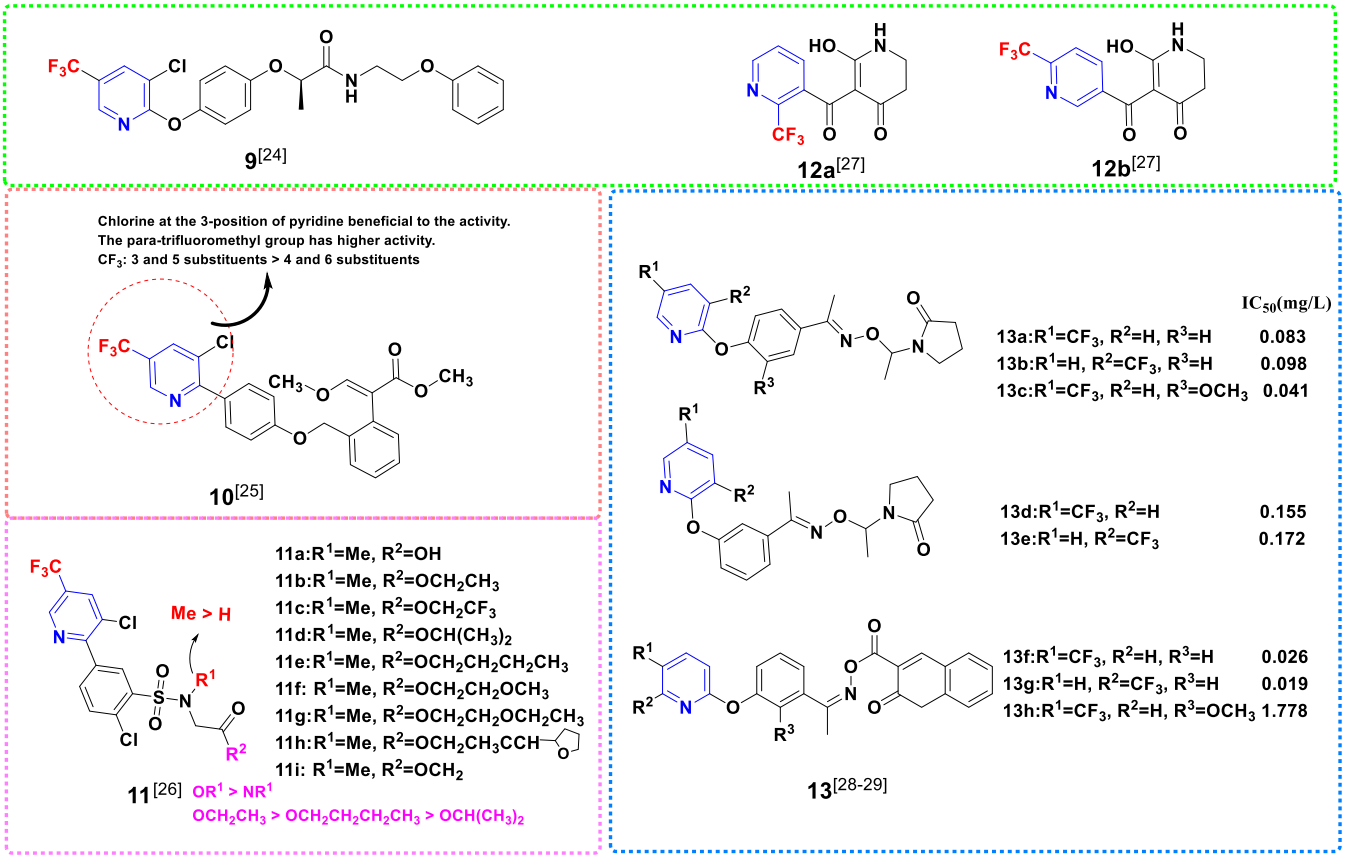

Figure 5. TFMP fragment-containing derivatives with herbicidal activity.

1*H*-pyrazole and 1,3,4-oxadiazole together and prepared a series of unprecedented 1,3,4-oxadiazole derivatives (compound **22**) with excellent insecticidal activity.[42] Later, we changed the 3-chloropyridin-2-yl-1*H*-pyrazole group into a TFMP group and introduced different substituted phenyl rings on the other side of the 1,3,4-oxadiazole structure. A series of 1,3,4-oxadiazole derivatives (compounds **23** and **24**) containing a TFMP fragment were synthesized[43,44] and evaluated for insecticidal activities. Most of these compounds have 100% insecticidal activity against *Plutella xylostella* and *Helicoverpa armigera* at 500 mg/L. According to the SARs, different substituents or substitution patents on the benzene ring play crucial roles in insecticidal bioactivities. Particularly, installing an appropriate electron-withdrawing group on the 4 position of benzene benefits insecticidal activity. In addition, we also replaced 3-chloropyridin-2-yl-1*H*-pyrazole of chlorantraniliprole with TFMP to design and synthesize a series of phthalamide derivatives **25** and introduced a hydrazone substructure (−CONHN═CH−) to synthesize compound **26**.[45,46] Although inferior results were obtained in the bioactivity tests against insects, these molecules exhibited excellent antiviral activities (for more detail, see section 3.5). In addition, the introduction of a chiral sulfide can not only show good insecticidal activity against *Plutella xylostella* and *Ostrinia nubilalis* but also endeavor good antiviral activities against TMV. Similarly, the introduction of an acyl thiourea group or an acyl urea group (compounds **27** and **28**)[47,48] can also enhance their antiviral activities without any improvement in their insecticidal activities.

3.3. Antifungal Activity. Thus far, there are five commercial fungicides containing TFMP. As an important active fragment, TFMP was also important in the discovery of new fungicides in recent years. Bayer has proposed a series of TFMP-containing compounds with good antifungal activities.[49−55] The TFMP ring is installed with a phenoxy group at the 2 position and a triazole ethanol group at the 4 position (Figure 8). Compounds **29** and **30** were synthesized by Hoffmann et al.[50] and were used in the *in vivo* preventive test at 500 mg/L. Their efficacy against *Botrytis cinerea, Puccinia recondite, Sevtoria tritici, Uromyces appendiculatus, Alternaria, Phakopsora, Venturia, Blumeria, Levtosvhaeria nodorum, Puccinia triticina*, and *Sevtoria tritici* was not less than 90% compared to the control. Other related molecules can reach this level even at 100 mg/L, although with a relatively narrower antifungal spectrum. Sudau and Coqueron[51,53,54] introduced a pyridyloxy group to replace the phenoxyl group in this skeleton to afford the compounds **31**−**33**, which showed extremely broad antifungal activities in the *in vivo* tests. SAR investigations also suggested that TFMP had played important roles in antifungal bioactivities.

In 2016, Li and co-workers[56] introduced the substructure of strobilurin via benzyl ether to yield compound **34** (Figure 9), which had an excellent fungicidal activity of 80−90% against *Erysiphe graminis* at a concentration of 1.56 mg/L and was better than azoxystrobin (60%) and kresoxim-methyl (40%). Zhang and co-workers[57] demonstrated that the introduction of a −F or $-CF_3$ group to the pyridine ring could improve its antifungal activity and expand the antifungal spectrum, which is helpful to the development of novel antifungal agrichemicals. The compound **35** developed by Kahkashan et al.[58] exhibited greater than 80% antifungal activities against *Rhizopus tomato* and *Fusarium oxysporum* at the concentration of 100 mg/L

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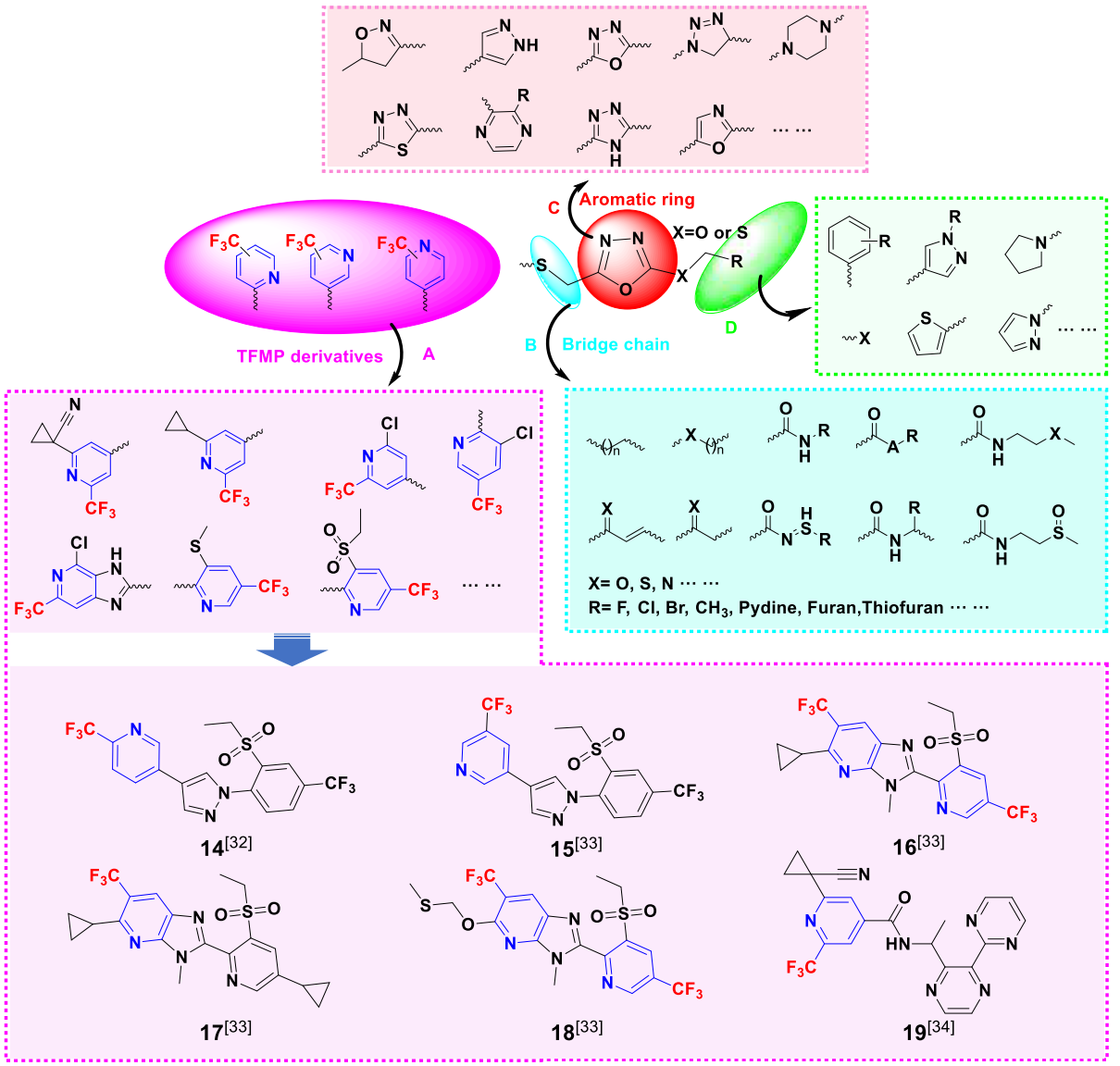

Figure 6. Derivatives with insecticidal activity containing TFMP fragments from Syngenta.

(Figure 9). The 3- or 5-substitution position of the $-CF_3$ group has little impact on the antifungal bioactivities. In contrast, the introduction of two or more chlorine atoms can increase the fungicidal activities of the afforded molecules.

2,8-Bis(trifluoromethyl)quinolines **36** (EC_{50} = 0.41 μg/mL) and **37** (EC_{50} = 0.55 μg/mL) showed excellent curative effects against *Sclerotinia sclerotiorum* in rapeseed.[59] The preliminary mechanism shows that they could cause changes in cell membrane permeability and the production and accumulation of reactive oxygen species, affect mitochondrial membrane potential, and effectively inhibit the germination and formation of sclerotia. Using fluopyram as a lead structure, Hua and co-workers[60] introduced a sulfur-containing chain optimized to yield compound **38** (Figure 9), which showed almost the same inhibition rate as fluopyram against *Botrytis cinerea*, *Colletotrichum capsici*, and *Phomopsis vexans*. It was found that antifungal activity could be enhanced via the bonds between TFMP and the Q site of succinate dehydrogenase (SDH). More recently, the guanidine structure was inserted into the structure of fluopyram to afford compound **39**. This compound processed both excellent antifungal and nematicidal activities. In particular, the antifungal activity on *Pythium aphanidermatum* (EC_{50} = 9.93 mg/L) was much better than that of fluopyram (EC_{50} = 19.10 mg/L).[61] Molecular docking studies indicated that the guanidine group formed strong hydrogen bonds with the amino acid residue on SDH.

3.4. Antibacterial Activity. Although there is no product containing TFMP structure launched as the bacterial agent thus far, the studies for the development of novel bactericides based on TFMP derivatives have aroused general concern and have been well-received step by step in recent years. Song's group designed and synthesized a series of TFMP-containing compounds by introducing oxadiazole sulfones (compound **40**; Figure 10)[62] or methoxybenzyl amino-1,3,4-thiadiazole (compound **41**; Figure 10)[63] via an ether linker. These types of compounds showed excellent antibacterial activity against *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), *Xanthomonas oryzae* pv. *oryzicola* (*Xoc*), and *Ralstonia solanacearum* (*Rs*) *in vitro*. Particularly, the EC_{50} value of compound **40f** (0.24 mg/L) was more than 375 times lower than those of the antibacterial agents thiodiazole copper (127.44 mg/L) and bismerthiazol (91.08 mg/L). Compound **40f** could significantly impact the

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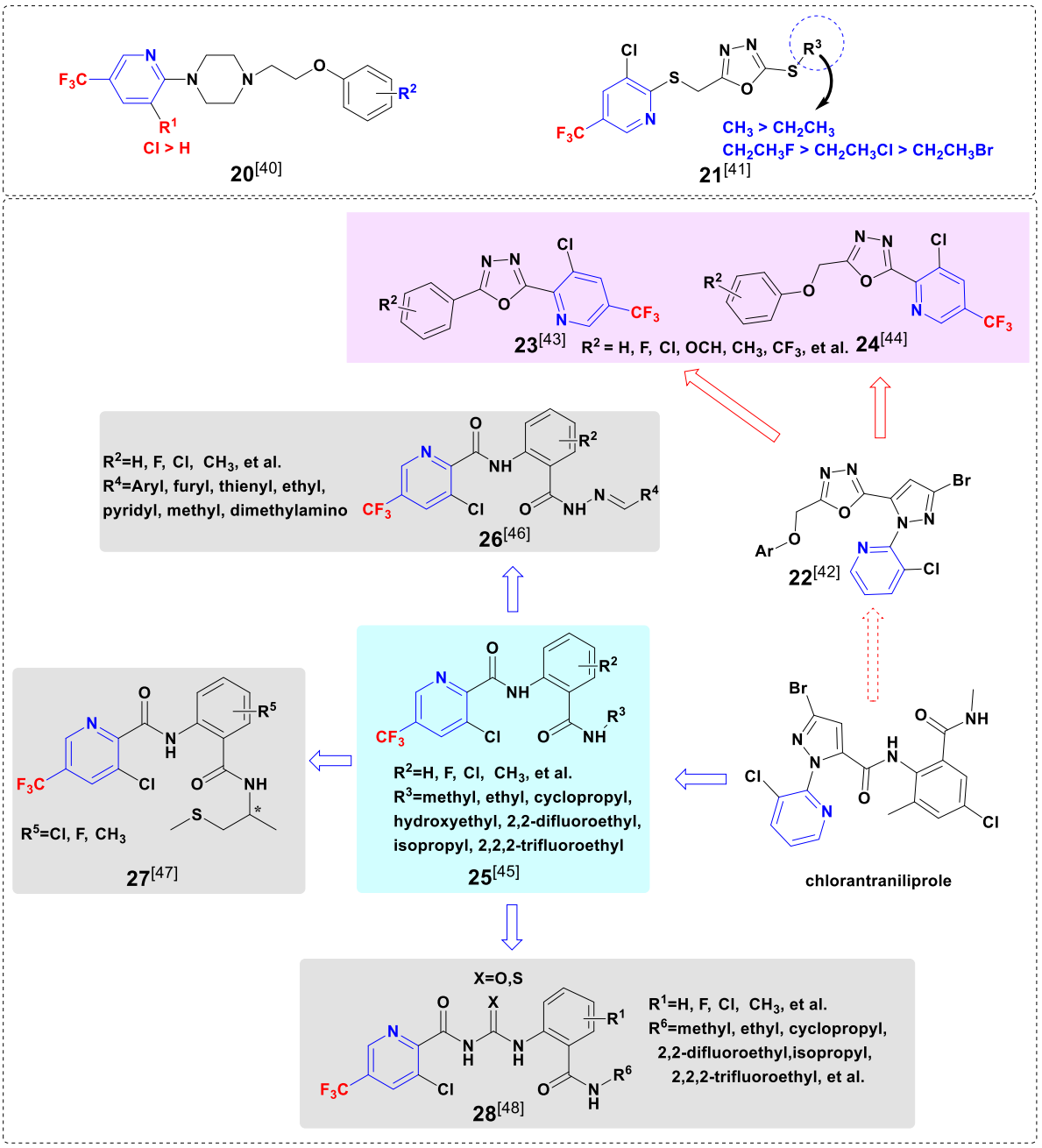

Figure 7. TFMP fragment-containing derivatives with insecticidal activity.

growth of *Xoo* cells by reducing extracellular polysaccharides, increasing the permeability of the cell membranes, and destroying the surface cell of *Xoo*. Moreover, thiadiazole derivatives containing both the TFMP structure and substituted benzamide were found to be extremely active against a variety of bacteria in plants. For example, the EC_{50} values of compounds **42a−42f** against *Xoo* are much lower than those of commercial fluopyram, fosthiazate, and copper thiazide. In addition, most of the derivatives have moderate to excellent antibacterial activities against *Xac* and *Rs*.

We have also found that TFMP-amide molecules containing sulfur atoms (e.g., sulfide, sulfone, sulfoxide, and *N*-cyano sulfonimide)[64−66] processed with certain antibacterial activities against *Xoo* and *Rs*. For instance, the EC_{50} values of the compounds **43a−43h** against *Rs* or *Xoo* varied from 40 to 83 mg/L, which were all lower than those of commercial copper thiodiazole and bimethiazole.

3.5. Antiviral Activity. TFMP derivatives have seldom been used as antivirus agents for plant protection. As we mentioned before (see section 3.2), compounds **44−47** have exhibited unexpectedly excellent antiviral bioactivities during our search for potential insecticides derived from TFMP cores.[46,47] Especially, the compounds **44** and **45** consisting of substituted anthranilic diamides and hydrazone/sulfide moieties showed excellent antiviral activities against tobacco mosaic virus (TMV). The EC_{50} value of the compound **44e** against TMV (0.076 mg/mL) is much lower than that of ninnanmycin (0.362 mg/mL). The mechanism investigations indicated that the strong hydrogen-bonding interactions (with amino acid residues of TYR139, ASN73, and ALA74), halogen interactions (with TYR72, ALA74, and PHE12), and $\pi-\pi$ T-

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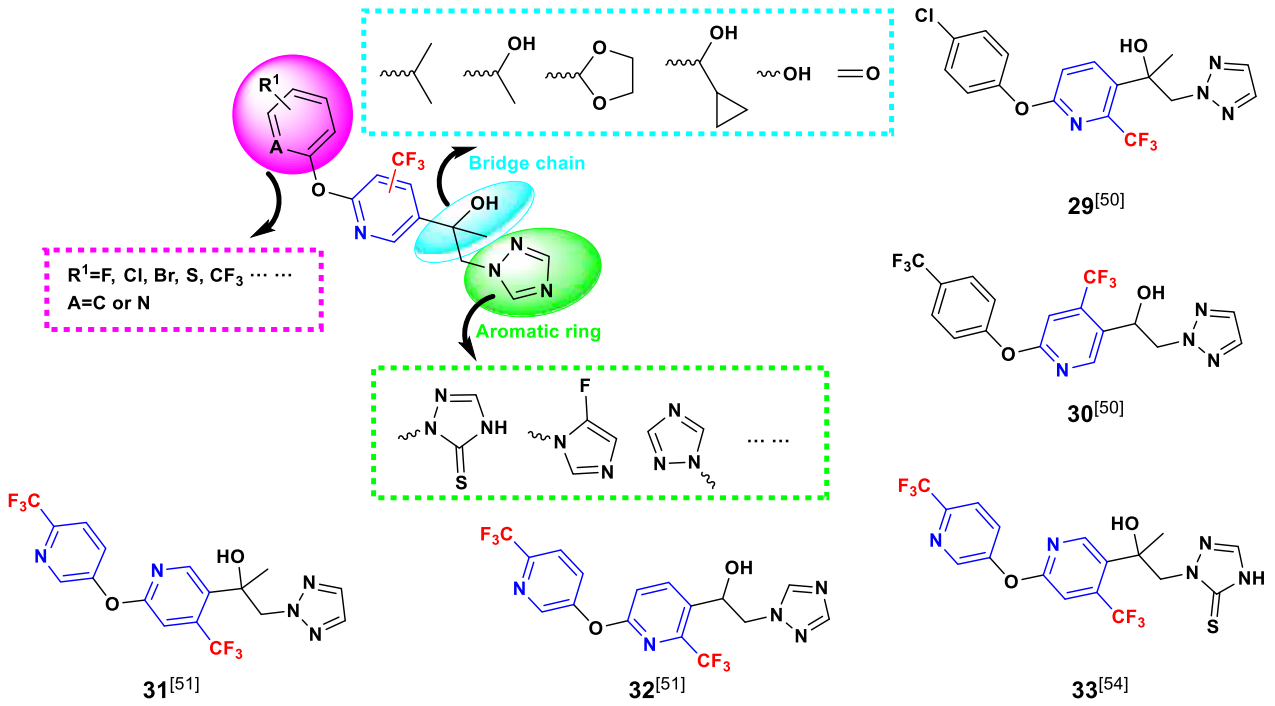

Figure 8. Derivatives with antifungal activity containing TFMP fragments from Bayer.

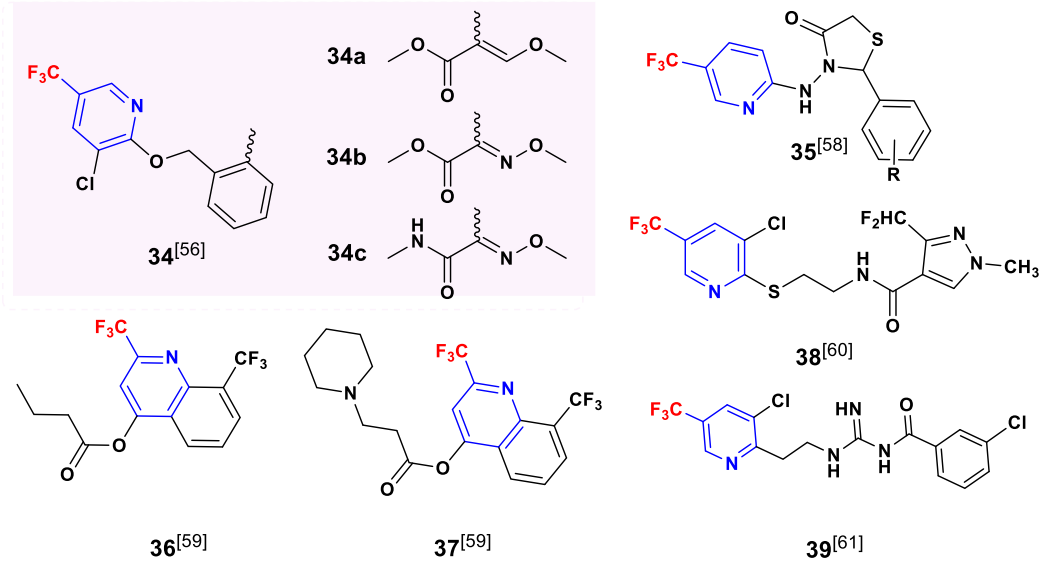

Figure 9. TFMP-containing molecules with antifungal activity.

shaped interaction (with PHE12) between active compounds and TMV coat protein (CP) could be observed (Figure 11B). These strong interactions could inhibit and impact the self-assembly of TMV particles.[67] Chiral compounds with different configurations also showed obvious distinctions on the antiviral bioactivities. The introduction of acyl urea or acyl thiourea as the connecting bridges (e.g., compounds **46** and **47**) was also beneficial to the antiviral activities via strong interactions with the TMV CP (Figure 11C) and effective inhibitions in the self-assembly of the RNA and CP of the TMV particles.[68] Moreover, it was found that the α-ketoamide derivatives bearing a TFMP ring also showed good activity against TMV via obstructing the self-assembly of TMV particles.[69]

4. SUMMARY AND OUTLOOK

Recent studies have shown that the introduction of different groups into active frameworks is still one of the most effective methods for the innovation of novel pesticides. TFMP has proven to be a promising active moiety in pesticide chemistry. The introduction of functional groups, such as amide, sulfide, sulfonyl, alkoxy, and heterocyclic groups, into TFMP can often provide derivatives with fantastic effects. Using the biological isotopic replacement strategy, replacing a substructure of commercial pesticide (such as chlorantraniliprole) with the TFMP structure could afford novel structures with efficient and broad-spectrum bioactivities. This provides an efficient avenue for the discovery of new active compounds. In addition, the application of TFMP in antibacterial and antiviral activities

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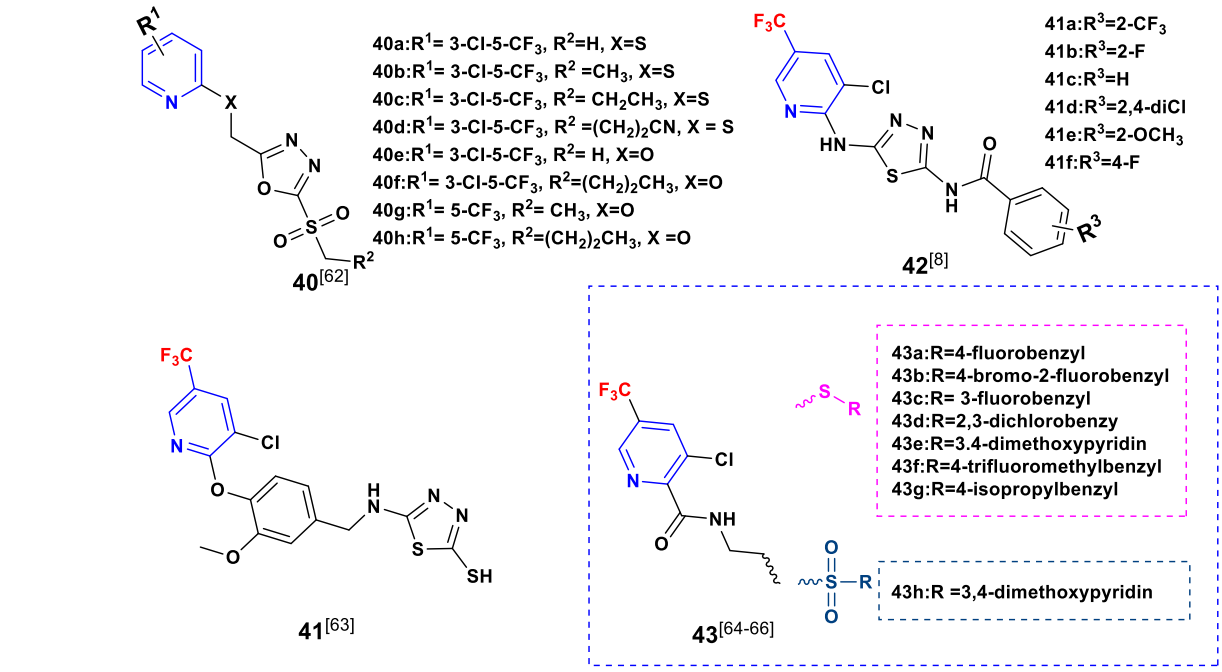

Figure 10. TFMP fragment-containing derivatives with antibacterial activity.

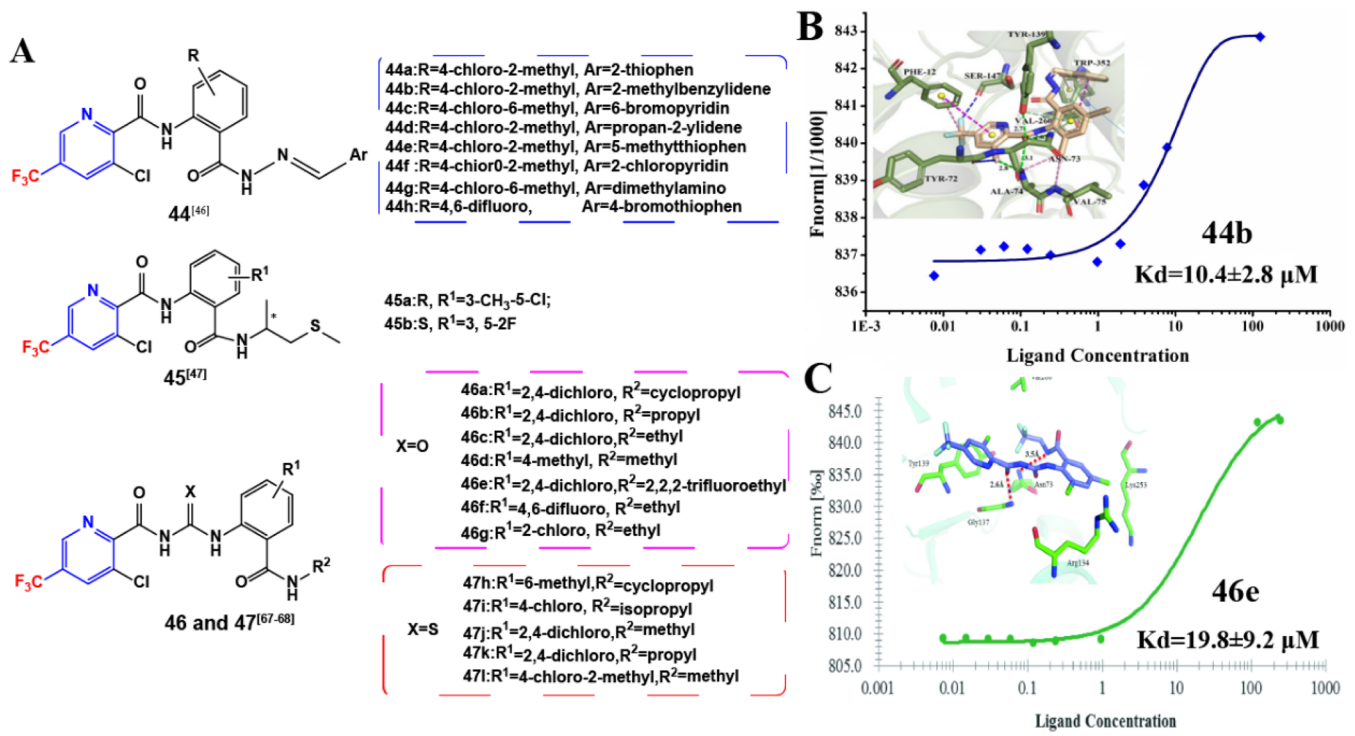

Figure 11. (A) TFMP-containing molecules with antiviral activity. Microscale thermophoresis (MST) measurement results and molecular docking studies of the compounds (B) **44b** and (C) **46e** with TMV CP.

is still relatively rare, and there is no commercialized variety thus far. Fortunately, some potential compounds have been discovered, and we believe it is still promising to discovery more active compounds. For example, with the installation and optimization of structures, such as acyl (thio)ureas and acylhydrazones, some compounds with excellent antiviral activities could be screened. Nevertheless, there is still a long way for these TFMP derivatives to enter the market.

Up to now, the relationship between the substitution position (or types) of trifluoromethyl (or other groups) on pyridine and the bioactivity is not well-understood, together with the facts that the mechanism (or targets) for most TFMP derivatives are also unclear. To a certain extent, these facts limit the in-depth optimization for their structures. Currently, bioisosteric replacement combined with SAR studies is still an important strategy for the optimization of TFMP compounds. Furthermore, it is crucial to understand the role that TFMP

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J. Agric. Food Chem. XXXX, XXX, XXX−XXX

played in the activity; some studies have used molecular docking to elucidate the roles of TFMPs in an active compound, which has been validated *in vitro* as well as *in vivo*.[67,68] These works provide a good basis for a rational design based on TFMP. Therefore, taking TFMP as the growth point of the active fragment and tools of fragment-based drug design (e.g., ACFIS),[70] reasonable designs by the introduction of different groups at different positions of the structure of TFMP could be an efficient strategy for discovery of active compounds. It is foreseeable that these technologies will accelerate the innovation of new pesticides containing TFMPs.

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Notes

The authors declare no competing financial interest.

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