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REVIEW

New chemical fungicides in relation to risk for resistance development

Hideo Ishii[1]

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Abstract
Fungicides have played a key role in crop disease control worldwide. However, resistance development in pathogen populations became a serious concern in as early as 1970s and has increased further in recent years. More stringent pesticide regulation based on precautionary principle has made the introduction of new chemistry challenging. Despite such difficulties, many fungicides have been developed successfully and some of them have novel mode of actions such as the inhibition of DHODH and GWT1. In this paper, the author reviews large numbers of literature on newly developed fungicides in relation to resistance. The approach to mitigate resistance which includes the application of non-fungitoxic disease resistance inducers, crop resistance breeding, and biocontrol is also discussed briefly.

Keywords DHODH inhibitors · DMIs · Fungicide resistance · GWT1 inhibitors · MBI-P · OSBPIs · QiIs · QoIs · Resistance inducers · SDHIs

Introduction

Over 50 years have passed since fungicide resistance became a major problem in crop disease control (Corkley et al. 2022; Dekker and Georgopoulos 1982; Ishii and Hollomon 2015; Thind 2012). To manage diseases and combat resistance, various types of fungicides have been developed and introduced into the market. However, 'a cat-and-mouse game' between fungicide discovery and resistance development in pathogens has been repeated continuously. In recent years, increasingly stringent pesticide regulation has made the introduction of new chemistry challenging, particularly in the EU where regulation is governed by hazard rather than risk (Phillips 2020). The endocrine-disrupting effects of azole fungicides were suspected (Draskau et al. 2019; European Food Safety Authority (EFSA) 2022; Taxvig et al. 2007, 2008; Tesh et al. 2019) and some fungicides such as epoxiconazole and propiconazole have been banned in France (Agriland 2019; Lynxee consulting 2019). The multi-site fungicides mancozeb and chlorothalonil, used as solo or in a mixture with single-site fungicides having different mode of actions, are widely used because they are regarded as essential tools to manage resistance (McGrath 2022; Thind and Hollomon 2018). However, regulation of these multi-site inhibitors also tightened due to their health and environmental concerns (Green et al. 2018; Health Canada 2020; Jones et al. 2020; Uppala et al. 2020) and they were banned in the EU (Irish Examiner 2021; Lynxee consulting 2019).

Other important concerns are that human-infecting pathogenic fungi are evolving resistance to all licensed anti-fungal drugs (Fisher et al. 2022). The large-scale agricultural use of azole fungicides, which share 20–25% of a world market (Jørgensen and Heick 2021), severely influenced development of multiple antimicrobial resistance in the human pathogen *Aspergillus fumigatus* (Fisher et al. 2018, 2022; Fraaije et al. 2020; Kang et al. 2022; Verweij et al. 2020). The use of azole fungicides to treat invasive Aspergillosis in people is being hampered by the spread of resistant genotypes (Doughty et al. 2021). The National Academies, USA, organized the workshop 'The role of plant agricultural practices on development of antimicrobial resistant fungi affecting human health' in June 2022 (https://www.nationalacademies.org/our-work/the-role-of-agricultural-practices-on-development-of-antimicrobial-resistant-microbes-affecting-human-health-a-workshop-series. Accessed 31 July 2022) indicating the depth of concerns about this matter in the society.

✉ Hideo Ishii
hi481204@yahoo.co.jp

[1] Faculty of Life and Environmental Sciences, University of Tsukuba, Tennodai 1-1-1, Tsukuba, Ibaraki 305-8572, Japan

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The EU has launched 'Farm to Fork strategy' (https://food.ec.europa.eu/horizontal-topics/farm-folk-strategy_en), a core component of the 'European Green Deal', recently, and declares that by 2030, the risk and use of pesticides should be reduced by 50%, and that at least 25% of the EU's agricultural lands shall be under organic farming (Feldmann et al. 2022; Purnhagen et al. 2021). Similar sort of approach has begun in other regions of the world, e.g., 'Strategy for Sustainable Food Systems, MeaDRI' in Japan (https://www.maff.go.jp/e/policies/env/ env_policy/meadri.html. Accessed 31 July 2022). Such a global environment surrounding agrochemicals stimulates demand for more selective, safer, resistance-breaking, and cost-effective chemicals (Lamberth et al. 2013). Moreover, the development of new classes of fungicides will be a key component in addressing the increasing resistance problem. General trends and strategies for novel pesticides have been summarized recently (Guo et al. 2021; Umetsu and Shirai 2020). Therefore, in this paper, the author provides a further review of the fungicides developed recently, studies on resistance to those products, and discusses the mitigation options for resistance.

Sterol demethylation inhibitors (DMIs, FRAC Code 3)

DMI fungicides, which inhibit biosynthesis of essential sterols in cell membranes, are one of the most important fungicide classes worldwide (Mehl et al. 2019) and consist of 37 compounds (Fungicide Resistance Action Committee (FRAC) 2022). Among them, mefentrifluconazole (Fig. 1A), developed by BASF, is particularly interesting

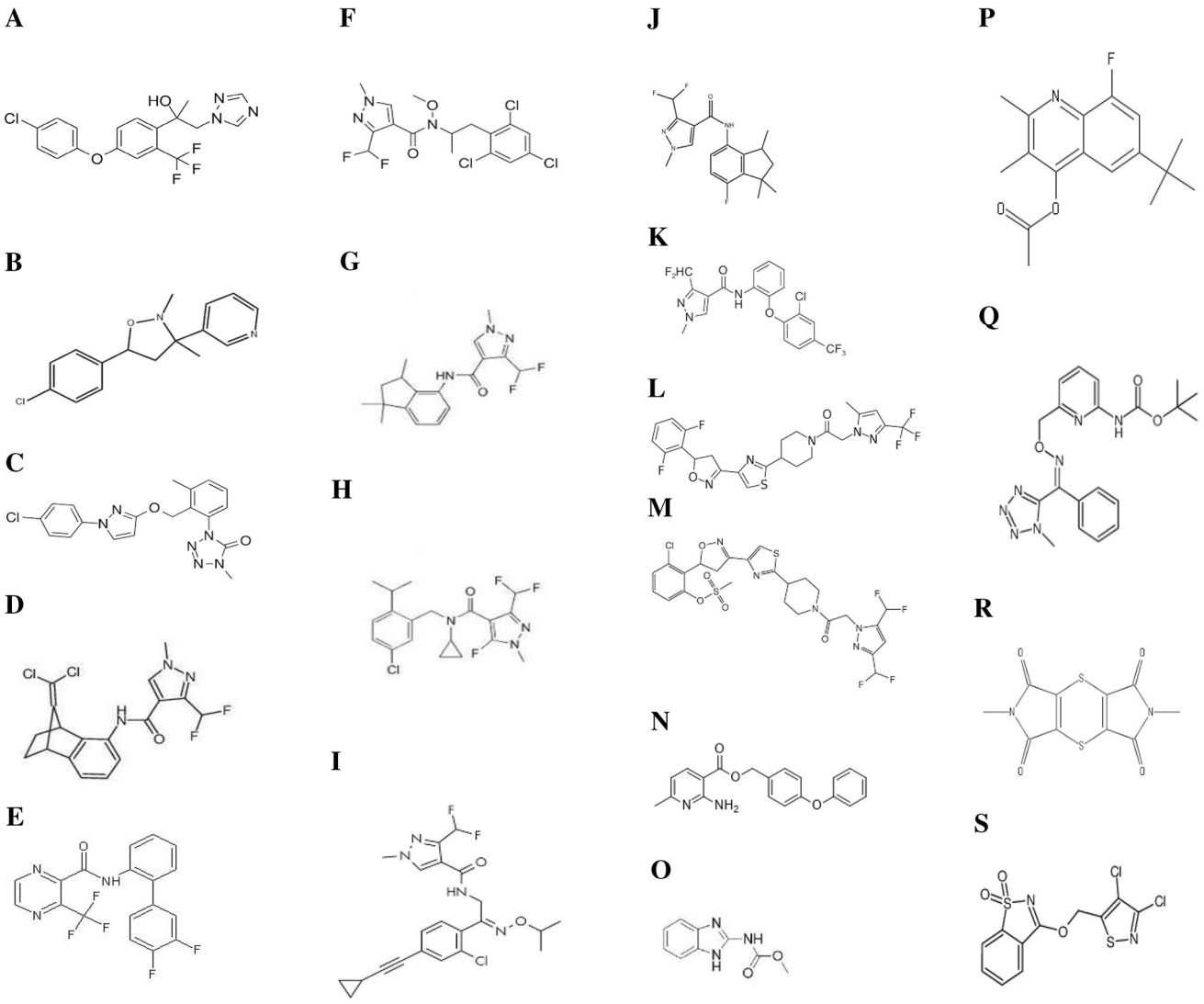

Fig. 1 Chemical structure of (**A**) mefentrifluconazole, (**B**) pyrisoxazole, (**C**) metyltetraprole, (**D**) benzovindiflupyr, (**E**) pyraziflumid, (**F**) pydiflumetofen, (**G**) inpyrfluxam, (**H**) isoflucypram, (**I**) pyraropoyne, (**J**) fluindapyr, (**K**) flubeneteram, (**L**) oxathiapiprolin, (**M**) fluoxapiprolin, (**N**) aminopyrifen, (**O**) pyridachlomethyl, (**P**) tebufloquin, (**Q**) picarbutrazox, (**R**) dipymetitrone, and (**S**) dichlobentiazox

because neither embryofetal toxicity nor teratogenicity has been shown for this fungicide with more favorable toxicity profile (EFSA 2018; Tesh et al. 2019). This fungicide revealed high efficacy to control key fungal diseases of pome and stone fruit, grapevine, potato, soybean and other crops (Gao et al. 2021; Heinecke et al. 2019; Li et al. 2021) and was recently registered (https://agriculture.basf.com/global/en/innovations-for-agri culture/innovation-for-fungicides/revysol.html. Accessed 31 July 2022).

Good control efficacy of mefentrifluconazole was found against a wide spectrum of existing triazole-resistant (referred to 'triazole-adapted' in literature) isolates of *Zymoseptoria tritici* of wheat (Jørgensen et al. 2020; Strobel et al. 2020). High intrinsic activity of mefentrifluconazole and a low correlation of resistance was observed with representative DMIs used for Septoria leaf blotch control such as prothioconazole and epoxiconazole (Strobel et al. 2020). The superior field performance of mefentrifluconazole did not seem to be influenced by the currently dominating CYP51 mutations (Jørgensen et al. 2020). However, the results from the *in vitro* testing showed strong cross-resistance between mefentrifluconazole, difenoconazole, and tebuconazole in this fungus subsequently (Heick et al. 2020). The presence or absence of cross-resistance between mefentrifluconazole and the other DMI fungicides was also examined using various fungi from different crops (Ishii et al. 2021). The sensitivity of *Monilinia fructicola* to mefentrifluconazole was higher than to difenoconazole, tebuconazole, and propiconazole. In contrast, the inhibitory activity of mefentrifluconazole was equal or slightly inferior in *Colletotrichum* spp., *Alternaria alternata* sp. complex and *Cercospora beticola*. In their study, cross-resistance to triflumizole, myclobutanil, and difenoconazole was clearly demonstrated on cucumber plants inoculated with powdery mildew (*Podosphaera xanthii*). Soon after that, Li et al. (2021) reported no evident correlation of the sensitivity to mefentrifluconazole and that to other DMIs on detached cucumber leaves inoculated with *Botrytis cinerea*. Mefentrifluconazole treatment resulted in the increase of mycelial branches, the decrease of ergosterol content and changes of the cell membrane permeability of this fungus. The high intrinsic activity of mefentrifluconazole against *Colletotrichum gloeosporioides* and *C. acutatum* sp. complexes was shown *in vitro* using baseline fungal isolates (Ishii et al. 2022). *In vivo* tests conducted on pepper fruit further exhibited protective and curative activity of mefentrifluconazole against pepper anthracnose caused by *C. scovillei* (Gao et al. 2021).

Pyrisoxazole (Fig. 1B) was developed by Shenyang Research Institute of Chemical Industry (SRICI) (Umetsu and Shirai 2020) and registered for the control of tomato gray mold caused by *Botrytis cinerea* in China. Stable mutants resistant to pyrisoxazole were generated via UV irradiation (RU-mutants) and spontaneous selection (RS-mutants) (Zhang et al. 2020). Positive cross-resistance was only observed between pyrisoxazole and the DMIs tebuconazole and prochloraz. The two-point mutations G476S and K104E, and the point mutation M231T were detected in the CYP51 protein of RU- and RS-mutants, respectively. Molecular docking suggested that G476S and M231T mutations led to the loss of electrostatic interactions between CYP51 and pyrisoxazole, while no change was found with the K104E mutation. Two point-mutations on CYP51 protein combined with induced expression of its target gene appeared to mediate the pyrisoxazole resistance of *B. cinerea* (Zhang et al. 2020).

Dihydroorotate dehydrogenase inhibitors (DHODHIs, FRAC Code 52)

The fungicide ipflufenoquin (Fig. 2A) was developed by Nippon Soda and has already been marketed to control many diseases of fruit trees and tea. Ipflufenoquin possesses a new mode of action that is the inhibition of dihydroorotate dehydrogenase (DHODH), a key enzyme in the biosynthesis of pyrimidine-based nucleotides (Fig. 2C) (Kuwahara et al. 2022; Madak et al. 2019). No cross-resistance to existing fungicides was observed, and ipflufenoquin revealed excellent field performance against *Venturia inaequalis* (apple scab), resistant to QoI and DMI fungicides (Nishino et al. 2021, 2022). Although its commercial products are not available yet, ipflufenoquin has also been registered for the control of gray mold, anthracnose, and powdery mildew of vegetables and/or beans as well as rice diseases. Very recently, another DHODH inhibitor quinofumelin (Fig. 2B), targeting the rice blast fungus *Pyricularia oryzae*, *B. cinerea*, scab, and anthracnose has been reported by Mitsui Chemicals Agro (Higashimura et al. 2022). Excellent activity of quinofumelin was further shown against *S. sclerotiorum* (Tao et al. 2021) and *Fusarium graminearum* inhibiting the mycotoxin deoxynivarenol (DON) biosynthesis of the latter fungus (Xiu et al. 2021).

As described above, azole resistance of the human pathogen *A. fumigatus* is a serious concern worldwide now. Very interestingly, olorofim (F901318), a novel orotamide antifungal compound showed potent activity against a broad range of pathogenic mold isolates including azole-resistant isolates of *A. fumigatus* (Escribano et al. 2022) by inhibiting DHODH (Andes 2022; Astvad et al. 2021; Oliver et al. 2016). Pyrimidine biosynthesis has also attracted attention as a target for the control of oomycete *Phytophthora infestans* which causes late blight of potato and tomato (Garavito et al. 2019; Garcia-Bayona et al. 2014) and *Pythium aphanidermatum* (Munier-Lehmann et al. 2013; Parker et al. 2001), and treatment of cancer cells (Madak et al. 2019; Zhou et al. 2021b). Resistance of *A. fumigatus* to olorofim was examined and only one of 976 clinical isolates exhibited

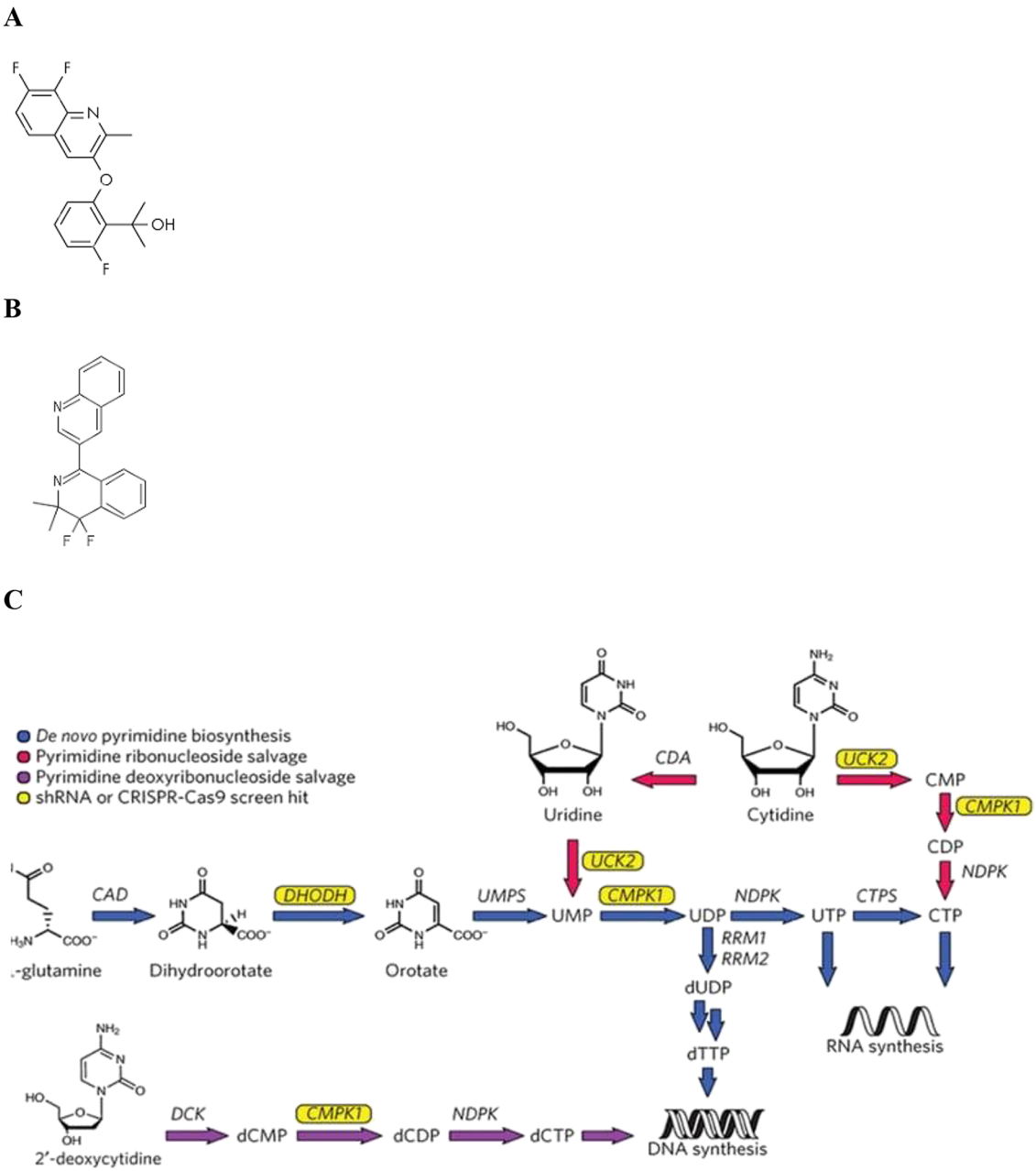

Fig. 2 Chemical structure of (**A**) ipflufenoquin, (**B**) quinofumelin, and (**C**) pyrimidine de novo biosynthesis pathway (https://microbenotes.com/de-novo-pyrimidine-synthesis/)

reduced sensitivity (Buil et al. 2022). Olorofim resistance was then induced under laboratory conditions and was associated with the point mutations G119A/C/F/Y/S/V/P at locus G119 of the *PyrE* gene encoding DHODH (Buil et al. 2022).

Inhibitors of DHODH and their uses in treatment against malaria, bacteria, coccidia, or fungi in the humans were reviewed previously (Munier-Lehmann et al. 2013). However, ipflufenoquin use may cause cross-resistance to olorofim in *A. fumigatus* and the risk of dual use of DHODH inhibitors in medical care and agriculture is now under discussion (Verweij et al. 2022). Human pathogenic fungi are evolving resistance to all licensed systemic antifungal drugs indicating that integrated responses need to be taken into consideration (Fisher et al. 2022). Resistance development is estimated medium to high risk for ipflufenoquin (FRAC 2022), so the risk assessment for dual use of DHODH inhibitors is urgently required.

Quinone outside inhibitors (QoIs, FRAC Code 11 & 11A)

QoI fungicides bind to the complex III (cytochrome bc1 enzyme) at Qo site (*cytb* gene) of mitochondria resulting in inhibition of respiration (Fisher et al. 2020; Sierotzki 2015; Sierotzki and Stammler 2019). Currently, 20 compounds are listed with **Code 11** in this group (FRAC 2022) and they share one of the major fungicide groups in the world. A new tetrazolinone fungicide metyltetraprole (Fig. 1C), developed by Sumitomo Chemical (Matsuzaki et al. 2020a; Yoshimoto and Arimori 2020) and belonging to **FRAC Code 11A**, has been registered in Japan for the control of major diseases such as scab and bitter rot of apple and leaf blight of sugar beet as a solo or a mixture with mancozeb.

Cross-resistance is generally observed among existing QoIs but metyltetraprole seems to be quite unique because its mode of action is not affected by the G143A and F129L mutations in *cytb* genes, the major cause of QoI resistance (Matsuzaki and Iwahashi 2020; Suemoto et al. 2019). This fungicide showed good performance against both *Z. tritici* and *Pyrenophora teres* which causes barley net blotch in the presence of high proportions of QoI-resistant strains in the field. The antifungal activity of metyltetraprole was unaffected by the G143A mutation in the pyraclostrobin-resistant isolates of *Z. tritici* in inoculation tests conducted under greenhouse conditions (Suemoto et al. 2019). The only small difference in EC_{50} was recorded for metyltetraprole (Resistance Factor, RF = 1.5) between F129L-harboring isolates and wild-type isolates of *P. teres* (Matsuzaki et al. 2022). In microtiter plate tests using liquid medium and *in planta* tests, the isolates of *C. beticola* were all sensitive to metyltetraprole regardless differential levels of sensitivity to trifloxystrobin (Matsuzaki et al. 2021). The high activity of metyltetraprole was further demonstrated against isolates carrying the rare cytb haplotypes G137R (*P. tritici-repentis*, the cause of wheat tan spot), G137S (*V. effusa*, the causal agent of pecan scab), L299F, N256S + L299F, and L275F + L299F (*Puccinia horiana*, the pathogen of chrysanthemum white rust) (Matsuzaki et al. 2022).

In enzyme assays using mitochondrial membrane preparations from *Z. tritici*, metyltetraprole strongly bound to cytochrome bc1 complex, whereas the activity was much weaker for azoxystrobin and pyraclostrobin (Craig et al. 2020). Binding mode at the Qo sites of *Z. tritici* homology models was proposed. The difference in wild-type (WT) and G143A binding energies (kcal/mol) was more negative for metyltetraprole than for azoxystrobin and pyraclostrobin, which was consistent with the difference in the measured resistance factors between resistant and WT isolates (Craig et al. 2020).

The following QoI fungicides have been developed in China: coumoxystrobin (SRICI), enoxastrobin (SRICI), flufenoxystrobin (SRICI), triclopyricarb (SRICI), and fenaminstrobin (SRICI). However, little information is available yet regarding pathogen resistance.

Quinone inside inhibitors (QiIs, FRAC Code 21)

QiI fungicides act at the quinone-inside (Qi) binding site of the complex III (cytochrome bc1 enzyme) in mitochondrial respiration chain. The target of this class of fungicides such as cyazofamid and amisulbrom was limited to diseases caused by oomycete pathogens, e.g., late blight of potato and tomato (*P. infestans*) and downy mildew of grapevine (*Plasmopara viticola*) (Gisi and Sierotzki 2015). However, new QiI fungicides, effective against ascomycete and basidiomycete pathogens such as *Z. tritici* and *Puccinia triticina*, respectively, have been developed recently (Owen et al. 2017; Yao et al. 2021).

The antifungal antibiotic UK-2A (Fig. 3A) and its analogs were isolated originally from the fermentation broth of the actinomycete *Streptomyces* sp. by Meiji Seika Pharma (Ueki et al. 1996) and its mode of action was elucidated (Machida et al. 1999; Ueki and Taniguchi 1997). Subsequently, fenpicoxamid (Fig. 3B), an isobutyryl acetal derivative of UK-2A was developed by Corteva Agriscience, Agriculture Division of DowDupont (Owen et al. 2019, 2020). The picolineamide fungicides fenpicoxamid and florylpicoxamid (Corteva Agriscience, Fig. 3C) target the Qi site of the cytochrome bc1 complex, via their primary metabolites UK-2A and CAS-649, respectively (Young et al. 2018, 2020, 2022).

Baseline sensitivity of European *Z. tritici* populations was measured and found that the distribution of their fenpicoxamid sensitivities were unimodal. However, the sensitivity of the Irish fungal collection was significantly lower than the baseline collections and suggested to be associated with multi-drug resistance (Kildea et al. 2022). Baseline fenpicoxamid sensitivity was tested using QoI-resistant isolates of *Pyrenophora tritici-repensis* (tan spot of wheat) in Argentina (Sautua and Carmona 2022). Baseline sensitivity of *B. cinerea* and control efficacy against gray mold were also examined for florylpicoxamid exhibiting strong activity (Li et al. 2022c).

Risk assessment was conducted for resistance development to fenpicoxamid. In the yeast *Saccharomyces cerevisiae*, amino-acid substitutions N31K, G37C, and L198F at the Qi-quinone binding site of cytb reduced sensitivity to fenpicoxamid, UK-2A, and antimycin (Young et al. 2018). No cross-resistance was observed between QoI fungicides and fenpicoxamid in the field isolates of *Z. tritici* (Fouché et al. 2020; Kildea et al. 2022; Young et al. 2018). As the most likely fenpicoxamid resistance mechanism in *Z. tritici*, the G37V change was identified within the cytb Qi site (Fouché et al. 2020; 2022). At the Qi-binding site, glycine 37 is very near UK-2A in its proposed binding pose and the

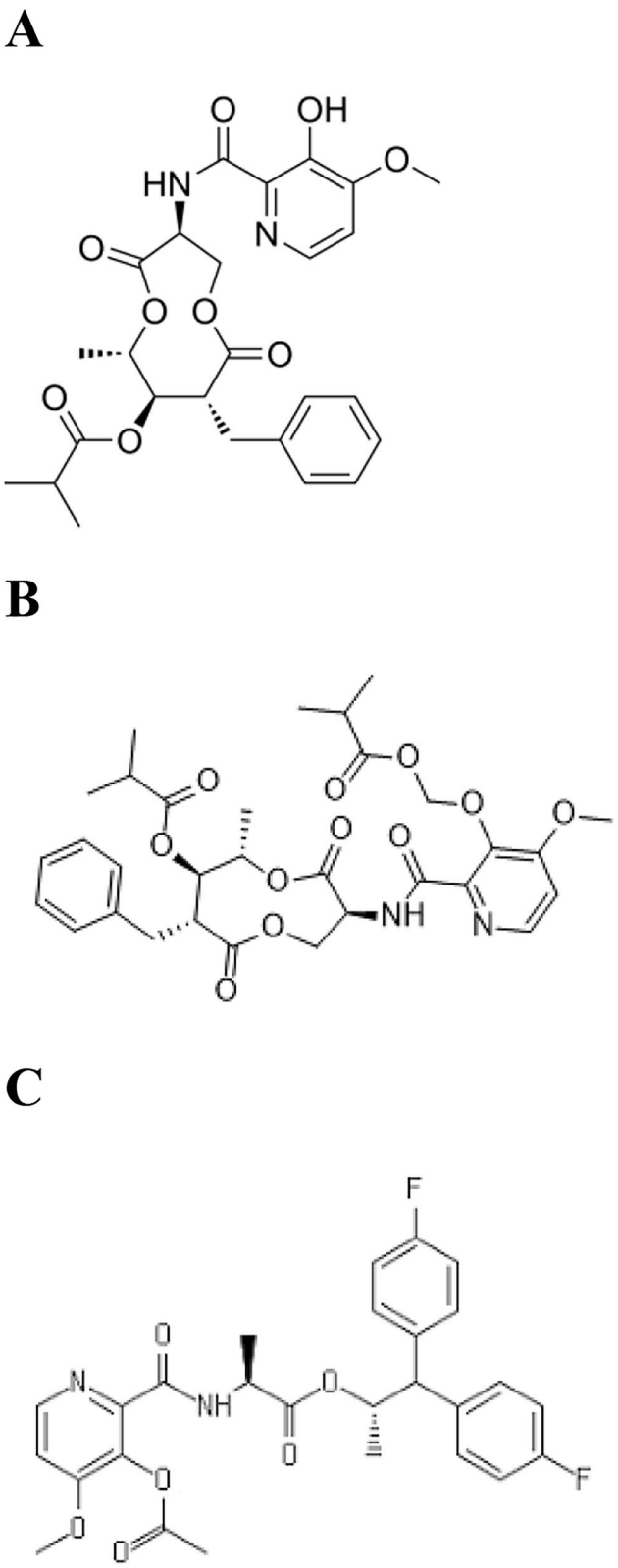

Fig. 3 Chemical structure of (A) UK-2A, (B) fenpicoxamid, and (C) florylpicoxamid

substitution of glycine by valine introduces a much bigger isopropyl group, which may interfere with UK-2A binding (Fouché et al. 2020). All the resistant strains could grow on medium containing fenpicoxamid with an alternative oxidase (AOX) inhibitor, excluding AOX overexpression as a resistance mechanism. In *Rhizoctonia solani*, the change L198F was involved in the low sensitivity to UK-2A *in vitro* (Avila-Adame et al. 2019).

Quinone outside inhibitor, stigmatellin binding type (QoSI, FRAC Code 45)

Ametoctradin, developed by BASF, is the only commercialized fungicide in this class (Gold et al. 2011). The binding mode of this oomycete fungicide differs from other fungicides such as the QiI cyazofamid, amisulbrom, and QoI fungicides (Dreinert et al. 2018). Instead, ametoctradin was thought to bind to the mitochondrial bc1 complex similarly to the Qi-site inhibitor stigmatellin (Fehr et al. 2016). This explains the lack of cross-resistance with strobilurins and related inhibitors, where resistance is mainly caused by G143A amino acid change. Subsequently, it has been proposed to classify ametoctradin as 'QioI' rather than QoSI because this fungicide interacts with both the Qi and Qo sites of cytb (with a better affinity for the Qi site) (Dreinert et al. 2018; Fontaine et al. 2019).

Resistance risk of ametoctradin is assumed to be medium to high (FRAC 2022). Many populations of *P. viticola* collected in French vineyards showed a reduction in sensitivity to ametoctradin and cyazofamid, and the former was correlated with the S34L change in cytb. In contrast, the *cytb* gene of cyazofamid-resistant strains contained L201S change and a six-nucleotide (ATGAGG) insertion at position 604 leading to protein modification with two amino acids (E203-DE-V204) in the Qi site of cytb (Cherrad et al. 2018; Mounkoro et al. 2019). A second type of insertion, the E203-VE-V204, was detected from strains which showed resistance to cyazofamid and amisulbrom but not to ametoctradin (Zito et al. 2020). For *P. viticola*, isolates harbouring G143A and S34L mutation were detected, and the AOX-related resistance seemed to increase within pathogen populations (Fontaine et al. 2019; Panon et al. 2018). When AOX is overexpressed, isolates exhibit cross-resistance to all complex III inhibitors (Zito et al. 2020).

Succinate dehydrogenase inhibitors (SDHIs, FRAC Code 7)

This group of fungicides binds to the complex II (succinate dehydrogenase, SDH) of mitochondrial electron transfer pathway resulting in inhibition of respiration (Klappach and Stammler 2019). Currently, 24 chemicals are grouped in SDHIs according to FRAC (2022), they have recorded

the greatest growth in the market and are taking share from QoIs due to resistance issues (Phillips 2020). Resistance to SDHIs has also increased in large number of fungal pathogens (Klappach and Stammler 2019; Stammler et al. 2015).

Fluopyram, developed by Bayer CropScience, revealed a strong inhibitory activity against not only the boscalid-sensitive but also highly boscalid-resistant isolates of *A. alternata* in pistachio (Avenot and Michailides 2010; Avenot et al. 2014) as well as *Corynespora cassiicola* in cucumber (Ishii et al. 2011) and its relation to the molecular mechanism of boscalid resistance was explained. Subsequently, isofetamid was developed by Ishihara (Tsukuda 2014; Zuniga et al. 2020). Absence of the cross-resistance to fluopyram and/or isofetamid was also reported from *B. cinerea* and some other pathogens (Avenot et al. 2012; Mallik et al. 2014; Veloukas and Karaoglanidis 2012; Veloukas et al. 2013; Walker et al. 2013).

The molecular mechanism of SDHI resistance was extensively studied and results indicated that the mutations leading to amino acid substitutions in the subunits B, C, and D of the SDHI fungicide-target are strongly involved in resistance (Adaskaveg et al. 2020; Avenot and Michailides 2010; Sang and Lee 2020; Lee et al. 2021a, b; Sierotzki and Scalliet 2013). Molecular docking of some SDHIs into the binding site was conducted using the homology models and suggested an important role of various amino acid polymorphisms in sensitivity to SDHIs (Amiri et al. 2020; Miyamoto et al. 2020; Shao et al. 2020). The active residue of fluopyram (benzamide moiety) resulted in different binding mode. In addition to the common binding sites B-W-235 and D-Y-117, fluopyram also forms hydrogen bonds with C-W-69 and C-S-73, thus increasing the binding energy and affinity between fungicide and protein (Zhu et al. 2022). Affinity binding studies with radio-labelled fluopyram revealed strong correlations among the affinity of SDHIs for SDH, SDH inhibition and *in vivo* growth inhibition in the wild type. Additionally, with site-directed mutagenesis that the *sdhB*^{H272Y} mutation, one of the most commonly found in field isolates of *B. cinerea*, did not affect SDH and respiration, whereas all the other mutations influenced against respiration by decreasing SDH actitivity (Lalève et al. 2014b). However, it was suggested that modifications causing a decline in the enzyme activity may be complemented by gene over expression in *C. cassiicola* (Shi et al. 2021).

In the recombinant mutants of *B. cinerea*, *sdhB* mutations affected SDH activity and respiration rate but displayed different effect on fitness (Lalève et al. 2014a). As suspected (Walker et al. 2013; Weber et al. 2015), the introduction of fluopyram increased the selection pressure and resulted in the appearance of isolates showing cross-resistance to boscalid and fluopyram (Amiri et al. 2014; Avenot et al. 2019; Vielba-Fernández et al. 2021; Zuniga et al. 2020). In Greek greenhouses with a fluopyran spray history, isolates harboring a novel *sdhB* mutation (I274V) were highly resistant to boscalid and fluopyam (Malandrakis et al. 2022).

Benzovindiflupyr (Fig. 1D) was developed by Syngenta (Guicherit et al. 2013) and also has distinct characteristics from existing SDHIs. *Colletotrichum* species, which cause anthracnose diseases on many crops, are insensitive (naturally resistant) to boscalid, fluxapyroxad and fluopyram. In contrast, benzovindiflupyr showed broad-spectrum *in vitro* and *in vivo* efficacy within the *Colletotrichum* genus (Carraro et al. 2020; Ishii et al. 2016, 2022; Oliveira et al. 2020). Benzovindiflupyr could activate more distinct mechanisms than boscalid and strongly affected hyphal membrane structure and function of *Colletotrichum* (Liang et al. 2022). These results were consistent with the previous finding that benzovindiflupyr damaged the cell membrane and increased mycelium electrolyte leakage of *Bipolaris maydis*, the causal agent of southern corn leaf blight (Hou et al. 2018b). The high activity of benzovindiflupyr was further demonstrated when tested using the isolates of *B. cinerea* resistant to boscalid, fluopyram, fluxapyroxad, and penthiopyrad (Hu et al. 2016) and boscalid-resistant isolates of *C. cassiicola* (Ishii et al. 2020; Zhu et al. 2021). With *Sclerotinia sclerotiorum*, the binding mode of benzovindiflupyr was compared with other SDHIs and results suggested that the diverse binding features with the SDH complex may be helpful for the design and development of highly effective broad-spectrum fungicides (Gao et al. 2020). The use of SDHI against *Phakopsora pachyrhizi*, the pathogen causing Asian soybean rust, increased rapidly, leading to a strong selection pressure for resistance to this group of fungicides (Godoy et al. 2016). As a result, resistance to benzovindiflupyr was reported in field isolates of this pathogen (Claus et al. 2022; Elis de Mello et al. 2021; Müller et al. 2021; Simões et al. 2018), *B. cinerea* (Zuniga et al. 2020), and *Z. tritici* (Hagerty et al. 2021).

The novel pyraziflumid (Fig. 1E) was developed by Nihon Nohyaku and launched in 2018 in Japan. This fungicide showed broad control efficacy against gray mold, powdery mildew, leaf mold, and other diseases (Kikutake et al. 2020). High control activity of pyraziflumid was also reported against *S. sclerotiorum*, the cause of Sclerotinia stem rot and *B. maydis* (Hou et al. 2018a, c).

Pydiflumetofen (Fig. 1F), developed by Syngenta, contains a new chemical group of N-methoxy-(phenyl-ethyl)-pyrazole-carboxamide and is a new broad-spectrum fungicide for multiple crops (Neves and Bradley 2019). Fusarium head blight of wheat, caused by *Fusarium asiaticum*, is one of the important target diseases for this fungicide (Hou et al. 2017). Resistance risk assessment was then performed in China (Chen et al. 2021). Highly (Pyd^{HR}) and moderately (Pyd^{MR}) pydiflumetofen-resistant isolates were generated on fungicide-amended culture medium in the laboratoty. SdhB^{H248Y} mutation was found from a Pyd^{MR} mutant,

whereas both $SdhC_1^{A64V}$ and $SdhC_1^{R67K}$ were from Pyd^{HR} mutants. Cross-resistance was detected between pydiflumetofen, boscalid, and thifluzamide, irrespective of types of mutation. In addition, all the resistant mutants produced the mycotoxin deoxynivalenol (DON) more than wild type isolate. The similar risk assessment was also conducted previously in China (Sun et al. 2020). In this study, resistant mutants were generated by both spontaneous selection and UV irradiation. Cross-resistance was found among pydiflumetofen, boscalid, and fluopyram but not found between pydiflumetofen and thifluzamide. *In planta* disease control was tested using mutant isolates carrying A83V in FGSdhC, the most frequent mutation *in vitro*, in the experimental field. The effectiveness of pydiflumetofen against the mutant was inferior to that against a sensitive isolate. The control efficacy on the other type of mutants (SdhC-R86H/C) was unknown. The related studies on this fungicide were also conducted with *B. cinerea* (He et al. 2020; Li et al. 2022b; Zhao et al. 2022), *A. solani* (Budde-Rodriguez et al. 2021), *S. sclerotiorum* (Duan et al. 2019; Zhou et al. 2021a), *C. zeae-maydis* (the causal fungus of corn gray leaf spot) (Neves and Bradley 2019), and *V. inaequalis* (Ayer et al. 2019).

Inpyrfluxam (Fig. 1G) was developed by Sumitomo Chemical (Watanabe et al. 2020a, b). The antifungal activity of this fungicide shows a broad spectrum against ascomycete and basidiomycete pathogens such as *V. inaequalis*, *V. nashicola* (the cause of Asian pear scab), *R. solani*, *S. rolfsii*, *Ustilago maydis* and *Puccinia allii* (Kurahashi 2021). Inpyrfluxam has been registered in Japan followed by the USA, Canada (https://www.sumitomo-chem.co.jp/news/detail/20200901.html) and Brazil where rust and leaf spot of soybean are targeted (https://www.sumitomo-chem.co.jp/news/detail/20220523.html). Baseline sensitivity of *V. inaequalis* was examined and mycelial growth inhibition was highest for inpyrfluxam followed by benzovindiflupyr, pydiflumetofen, and fluxapyroxad (Ayer et al. 2019).

Isoflucypram (Fig. 1H), developed by Bayer CropScience, possesses altered binding mode in the ubiquinone binding site of SDH (Desbordes et al. 2020). This fungicide efficiently controls all relevant leaf diseases in cereals, namely, leaf blotch, net blotch, brown and yellow rust (Bartholomaeus et al. 2021). As a new other SDHI fungicide, pyrapropoyne (Nissan Chemical, Fig. 1I) belonging to the pyrazolecarboxamide group is under development for paddy rice (Umetsu and Shirai 2020). Fluindapyr (Isagro/FMC, Fig. 1J) is highly effective in controlling a broad range of diseases in row and specialty crops, as well as turf (https://investors.fmc.com/news/news-details/2021/FMC-Corporations-fluindapyr-fungicide-receives-U.S.-EPA-registration/default.aspx. Accessed 31 July 2022) such as Asian soybean rust, scab, pink snow mold, and powdery mildew (http://sitem.herts.ac.uk/aeru/ppdb/en/Reports/3249.htm. Accessed 31 July 2022).

Flubeneteram (Fig. 1K) was successfully obtained by pharmacophore-linked fragment virtual screening (PFVS), a high-throughput drug discovery approach independent of biophysical screening techniques, in Central China Normal University (Zeng et al. 2022). This fungicide binds to SDH and is effective against rice sheath blight and cucumber powdery mildew.

Oxysterol-binding protein inhibitors (OSBPIs, FRAC Code 49)

Oxathiapiprolin (Fig. 1L), developed by DuPont, is a new class of oomycete fungicide based on a piperidinyl thiazole isoxazoline core and its mode of action is the inhibition of a novel target-an oxysterol binding protein which constitutes lipid transfer proteins (Olkkonen 2013; Pasteris et al. 2016). Excellent preventive, curative and residual efficacy was shown against key diseases of grapevine, potato, and vegetables, caused by oomycete pathogens (Miao et al. 2016b; Perotin et al. 2015). Oxathiapiprolin affected all stages in the asexual life cycle of *Pseudoperonospora cubensis*, the causal agent of cucurbit downy mildew, with trans-laminar activity, and movement from the root system to the foliage (Cohen 2015). The deployment of oxathiapiprolin will combat the mefenoxam-insensitive isolates of *P. infestans*, dominating in the field (Cohen et al. 2018).

However, oxathiapiprolin possesses medium-to-high risk of resistance development (FRAC 2022; Li et al. 2020). Resistant isolates were generated in the laboratory by UV light mutagenesis and mycelial adaptation of *P. capsici* (Miao et al. 2016a; Mboup et al. 2022) and *P. nicotianae* (Bittner et al. 2017). Isolates of *P. infestans*, *P. viticola*, and *P. cubensis* with resistance to oxathiapiprolin were also detected in field trial sites where performance of this fungicide was reduced or questioned (Keinath 2022; Mboup et al. 2022). Separately, resistant isolates were found from commercial fields in *P. viticola* in some European countries and China, in *P. infestans* in Indonesia and Colombia, and in *P. cubensis* in Korea and China (FRAC 2022; Knight et al. 2020; Massi et al. 2023).

Regarding genetic mechanisms of the resistance, a number of amino-acid substitutions of L733W, S768I/F/K/Y, G770A/I/P/V/L, N837I/F/Y, G839W, P861H, L863W/F, and I877F/Y were detected in OSBP from UV mutagenesis mutants of *P. capsici* (Andreassi et al. 2013). Some of these mutations, e.g., G770V, N837I and L863W were detected in resistant isolates of *P. viticola* from the field where poor disease control was observed after oxathiapiprolin had been continuously used for 4 years (Mboup et al. 2022). In addition to N837I, target site mutations of G770I, V820G, and I877F have been found in resistant isolates (FRAC 2022). In the case of the field isolates of *P. viticola*, the three substitutions L863W, N837I, and G770V were distributed unequally

depending on the trial sites, and a resistance factor for one bulk isolate carrying N837I exceeded 1000 (Mboup et al. 2022).

Mutation G686V and deletion of two amino acids, glycine (codon 734) and phenylalanine (codon 735) were also found in *P. nicotianae* resistant isolates produced by UV irradiation (Bittner et al. 2017). S768Y, G770V, G839W, and L863W, most frequent among the mutations in the OSBP gene, were associated with high resistance of the laboratory-induced resistant isolates of *P. capsici* (Mboup et al. 2022). G769W (changed to G839W) and G700V (changed to G770V) were reported in the OSBP gene of laboratory-adapted resistant isolates of *P. capsici* (Miao et al. 2016a, 2018). Transformation experiments and expression analysis confirmed the responsibility of G839W for the resistance. Furthermore, the molecular methods of allele-specific PCR (AS-PCR) and cleaved amplified polymorphic sequences (CAPs) were developed to identify G769W resulting in detection of resistance in the field (Miao et al. 2016a). Genome editing using CRISPR/Cas9 system further confirmed that G770V and G839W in OSBP confer resistance in *P. capsici* (Miao et al. 2018). In *P. sojae*, L733W, S768F/Y, N837Y/F, P861H, L863W, and I877Y in OSBP confer high resistance to oxathiapiprolin (Miao et al. 2020b). For *P. infestans*, N837I and G770V mutations were present at the OSBPI target site of resistant field isolates (FRAC 2022). The target site mutations I877F, G770V, and L863W were detected from field isolates of *P. cubensis* (FRAC 2022).

Among pathogens, different *Pythium* species revealed different oomycete fungicide sensitivities, and oxathiapiprolin was only effective against *P. splendens* and *P. ultimum*. This fungicide did not inhibit the growth of the other 14 *Pythium* species including *P. aphanidermatum*. Interestingly, oxathiapiprolin, registered in China to control tomato late blight, did not control *P. oligandrum* (Miao et al. 2020a). To discover new lead compounds for combatting oxathiapiprolin resistance, the 3D structure of OSBP from *P. capsici* was built using the homology modelling methods, and interaction of the OSBP with oxathiapiprolin was studied (Li et al. 2020).

Another OSBP inhibitor fluoxapiprolin (Fig. 1M) was developed by Bayer CropScience but has not been registered yet (Miao et al. 2021). There have been no reports of field resistance in *P. capsici*. However, fluoxapiprolin-resistant isolates of *P. capsici* with RFs ranging from 4 to 3467, were obtained by fungicide adaptation in the laboratory and cross-resistance between fluoxapiprolin and oxathiapiprolin was observed in these isolates. Five genotypes with seven heterozygous point mutations, G770V, △N835, N835S + I877F, N837I, and N837T + S910C, were found in OSBP (referred to PcORP1)-resistant isolates (Miao et al. 2021). Level of resistance differed depending on the genotypes, and isolates containing G770V or N835S + I877F showed high resistance (RF > 200). Importantly, simultaneous occurrence of two point-mutations resulted in high fluoxapiprolin resistance. For *P. infestans*, S768I + N837I, S768I + L860I, S768I, and I877F were found in OSBP of laboratory-induced resistant mutants (Li et al. 2022a). Positive cross-resistance was detected between fluoxapiprolin and oxathiapiprolin, and S768I + N837I or S768I + L860I point mutation types could cause high resistance in *P. infestans* (Li et al. 2022a).

Melanin biosynthesis inhibitors (MBIs, FRAC Code 16.1, 16.2, and 16.3)

Some fungal pathogens, such as rice blast fungus (*P. oryzae*) need melanin biosynthesis prior to host penetration through their appressoria. Until recently, MBIs have been divided into two groups, MBI-R (**FRAC Code 16.1**) and MBI-D (**FRAC Code 16.2**) inhibitors, which block hydroxynaphthalene reductase and scytalone dehydratase, respectively. Tricyclazole, a MBI-R inhibitor, has been used successfully with no clear evidence of resistance development in paddy fields. In contrast, the MBI-D inhibitor carpropamid caused a serious problem in blast control due to resistance (Takagaki 2015). Cross-resistance was observed between carpropamid and the other MBI-D inhibitors diclocymet and fenoxanil.

Subsequently, a new MBI fungicide tolprocarb (Fig. 4A) was developed by Mitsui Chemicals Agro and launched for rice blast and other disease control (Hagiwara 2019; Hagiwara et al. 2019). The principle mode of action of this fungicide has been revealed to be the inhibition of polyketide synthase (MBI-P, **FRAC Code 16.3**), involved in the early step of melanin biosynthesis pathway (Fig. 4B). No cross-resistance was observed in MBI-D resistant isolates of *P. oryzae* to tolprocarb. Surprisingly, tolprocarb was also effective against bacterial diseases of rice including bacterial leaf blight caused by *Xanthomonas oryzae* pv. *oryzae* where melanin was not involved in pathogen infection. Furthermore, tolprocarb induced systemic acquired resistance (SAR) in rice through accelerating some pathogenesis-related (PR) genes related with salicylic acid (SA)-mediated signaling pathway (Hagiwara et al. 2020). Based on this double mode of action, MBI-P activity and induction of the host defense response, tolprocarb was thought to have a low risk of fungicide resistance (Hagiwara 2019) but still needs to be addressed by long term observation in the future.

GWT1 inhibitors

Aminopyrifen (Fig. 1N), a novel 2-aminonicotinate fungicide developed by Agro-Kanesho, has a novel mode of action which is the inhibition of GWT-1 protein in glycosylphosphatidylinositol-anchor biosynthesis (Hatamoto et al. 2019). This biosynthesis pathway is an essential cellular process to anchor mannoproteins to the cell wall of

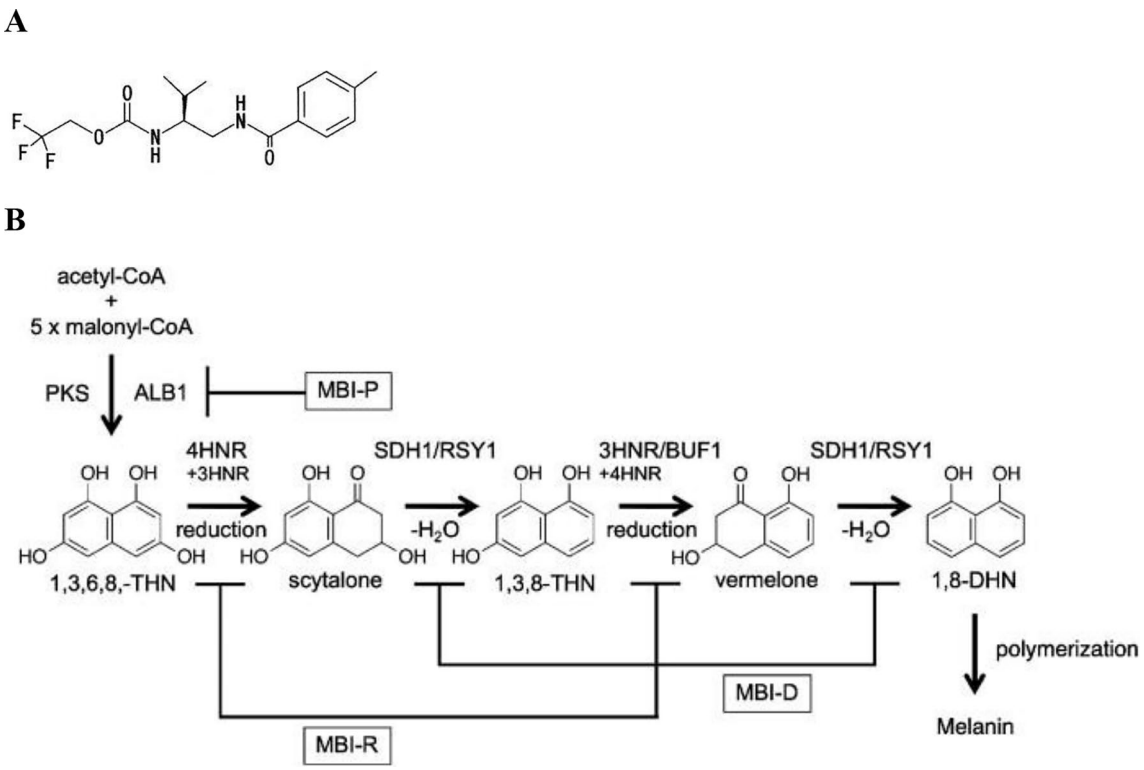

Fig. 4 Chemical structure of (A) tolprocarb, and (B) melanin biosynthetic pathway of *Pyricularia oryzae*. Inhibition points of the three groups of melanin biosynthesis inhibitors (MBIs) are shown. 1,3,6,8-THN, 1,3,6,8-tetrahydroxynaphthalene; 1,3,8-THN, 1,3,8-trihydroxynaphthalene; 1,8-DHN, 1,8-dihydroxynaphthalene (Motoyama et al. 2021)

fungi and has emerged as an attractive target for novel antifungals (Kapoor et al. 2020). Aminopyrifen shows strong activity against various ascomycete and basidiomycete fungi including *B. cinerea*, *B. graminis* f. sp. *tritici*, *P. xanthii*, and *Puccinia recondita* (Hatamoto et al. 2021), but the control efficacy of this fungicide seems to derive not only from strong mycelial growth inhibition but also from the reduced pathogenicity of fungal pathogens. This fungicide may inhibit maturation of proteins involved in the remodeling of cell wall polymers and pathogenicity.

As the fungicide fosmanogepix, the prodrug of manogepix targeting GWT-1 protein, is under clinical development currently, the large scale of aminopyrifen use may have a potential risk for cross-resistance emerging in human fungal pathogens (Verweij et al. 2022). Using the spontaneous mutants of *Candida glabrata* conferring reduced sensitivity to manogepix, the V163A mutation was found in the GWT-1 protein and suggested the importance of this valine residue to manogepix binding across different *Candida* species (Kapoor et al. 2020). The V163A *C. glabrata* and V162A *C. albicans* mutants showed cross-resistance to gepinacin, an unrelated molecule that targets fungal GWT-1. However, other non-target-based mechanisms most likely work as the mechanisms of resistance to manogepix in *C. krusei*.

Anti-tubulin agents (FRAC Code 53)

There are several anti-tubulin fungicides, i.e., benomyl, thiophanate-methyl, carbendazim (MBC, the active form of benomyl and thiophanate-methyl), thiabendazole (TBZ), diethofencarb, zoxamide, and ethaboxam. They are all classified as polymerization inhibitors. In contrast, pyridachlomethyl (Fig. 1O) developed by Sumitomo Chemical as a new type of anti-tubulin agent, promotes polymerization of tubulin and exhibited antifungal activity *in vitro* against many important pathogens including *Z. septoria*, *Pseudocercospora fijiensis*, *V. inaequalis*, *P oryzae*, and *B. cinerea* (Matsuzaki et al. 2020b). The differential expression levels of the gene encoding target β-tubulin as well as copy number of β-tubulin gene might be related to the difference in pyridachlomethyl sensitivity.

The carbendazim- or pyridachlomethyl-resistant mutants of *Z. septoria* were selected by UV mutagenesis in the laboratory (Matsuzaki et al. 2020b). Pyridachlomethyl was effective against carbendazim-resistant strains of *Z. septoria* and vice versa. Twelve of 17 mutants, showing resistance to pyridachlomethyl, had mutations in β-tubulin (Y222N/S and N219K) but the other five possessed mutations in α-tubulin (P325T/H/S and I355F). This was the first to report that mutations in not β- but α-tubulin can confer resistance to

fungicides. The target site of pyridachlomethyl is suspected to be located between α- and β-tubulin. It is a future subject to see whether the mutants obtained in the laboratory also appear in the field when pathogen populations are selected by this fungicide.

MOA unknown fungicides

Tebufloquin (Fig. 1P, **FRAC Code U16**), containing 4-quinolinol structure, was developed by Meiji Seika Pharma and released to the market for the control of blast, false smut, and brown spot of rice, purple stain of soybean, and gray blight of tea caused by *Pestalotia longiseta*. Tebufloquin was effective against the *P. oryzae* isolates, resistant to organic phosphates, the antibiotic kasugamycin, MBI-D, and QoI fungicides indicating the mode of action of tebufloquin is distinct from existing fungicides (Matsumura 2012). Both preventive and curative activity of tebufloquin will make its application flexible.

Picarbutrazox, developed by Nippon Soda is a novel fungicide containing tetrazolyl oxime structure (Fig. 1Q, **FRAC Code U17**) and has excellent control activity against *Pythium* diseases and downy mildew on various crops but not against ascomycete and basidiomycete fungi (Watanabe 2017). Cross-resistance was not observed between picarbutrazox and other commercial fungicides in cucumber downy mildew indicating a distinct mode of action of this fungicide. Picarbutrazox has preventive, translaminar and curative activity. At present, picarbutrazox is commercialized for the control of diseases caused by *Pythium*, *Fusarium*, and *Rhizopus* spp. on rice seedlings in addition to downy mildews of vegetable crops and *Pythium* disease on sugar beet.

Dipymetitrone is a novel organonitrogen heterocyclic compound (Fig. 1R) from Bayer CropScience (https://news.agropages.com/News/NewsDetail---13677.htm. Accessed 31 July 2022) and seems to be effective against Phytophthora rot, downy mildew, scab, early blight, and gray mold (http://sitem.herts.ac.uk/aeru/ppdb/en/Reports/3088.htm. Accessed 31 July 2022), but the details are unknown.

Resistance inducers

The practical use of disease-resistance inducers has a long history in agriculture with no resistance development in pathogens although it has not been well recognized. Blast caused by *P. oryzae* is one of the most devastating diseases in rice and recently in wheat (Castroagudin et al. 2015). Due to that, development of resistance to fungicides, e.g., MBI-D and/or QoI fungicides was repeated resulting in the rapid increase of market share of the three resistance inducers probenazole (**FRAC Code P 02**), tiadinil and isotianil (**FRAC Code P 03**) (Ishii 2015). The efficacy of tiadinil was also observed against wheat blast (Portz et al. 2021). For horticultural crops, acibenzolar-*S*-methyl (ASM, **FRAC Code P 01**) has been revived and expected to expand its registration. Recently, dichlobentiazox (Fig. 1S, **FRAC Code P 08**) was developed by Kumiai Chemical and it is effective against blast (Nagata et al. 2018; Terada et al. 2018), brown spot and other diseases including bacterial blight and bacterial grain rot of rice. The mode of action of this compound is induction of disease resistance through the activation of SA pathway (Terada et al. 2019).

The use of broad-spectrum but non-fungitoxic resistance inducers is a promising approach because the orchestrated mechanisms underlying induced SAR are less likely to be overcome easily by pathogens. The successful use of probenazole in Japan for the last nearly 50 years clearly demonstrates the great value of resistance inducers to mitigate pathogen resistance. Although phytotoxicity is the main limiting factor for resistance inducers in general, seed treatment as well as soil amendment with microencapsulated formulations was effective in reducing the risk for the phytotoxicity. Its long-lasting efficacy allows the application of typical fungicides to be reduced so that development of resistance in pathogens will also be minimized (Ishii et al. 2019). The use of resistance inducers has been mainly limited within Japan but the discovery of agrochemicals with potent plant immune-inducing activity has become an active research area recently in China (Guo et al. 2021).

Perspectives

As reviewed by Helepciuc and Todor (2022), alternative approaches to the intensive use of conventional chemical pesticides have gained political and public support worldwide. The most promising alternatives are integrated pest management (IPM) and organic farming including biocontrol. However, as the authors mentioned, adoption of IPM is not a dominant approach to agriculture yet not only in the EU but also in other parts of the world. The number of research papers on microbial biocontrol correlates with product approval. To promote low-risk alternatives and IPM, further efforts are needed. Therefore, development of novel chemical fungicides with higher safety to humans and environment, management of resistance, and integration with biocontrol will still be required for stable agricultural production (Lamberth et al. 2013). The speed-up of breeding sustainable disease resistance will also be necessary to minimize dependence on synthetic fungicides and lower risk of resistance. As briefly introduced by Ishii (2011, 2015), rice seeds of blast-resistant multi-lines were mixed and widely cultivated in the most important rice-growing region in Japan. As a result, the occurrence of blast dramatically decreased and blasticide applications were reduced to one fourth as compared before (Ishizaki 2008, 2010). Similarly, variety mixtures have proven to be a useful tool to diminish selection for fungicide resistance and virulence in wheat (Jørgensen 2023).

Declarations

Conflict of interest H. Ishii declares that he has no conflict of interest.

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